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Acute Kidney Injury in Severe Burns

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ACADEMIC DISSERTATION

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Pysähdy, analysoi, tee johtopäätös, jatka matkaa. *Juhani ”Lion #79” Tamminen*

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ABSTRACT

Severe burn injury is one of the most devastating traumas with its direct tissue destruction, triggering a systemic inflammation and numerous cytokine-mediated alterations of homeostasis. Acute kidney injury (AKI) is a common sequela in severe burns and substantially increases the risk of death. Known risk factors for the development of AKI are the size of the burn area, age, simultaneous inhalation injury, sepsis and use of nephrotoxic antibiotics. Early AKI develops often from a lack of sufficient kidney perfusion due to insufficient circulation or from rhabdomyolysis. Late onset AKI is often part of multiple organ failure (MOF), which is a gradually progressing, poorly manageable state. MOF is characterized by abruption in coagulation, oxygenation of lungs and kidney function. The focus of this thesis was to investigate novel biomarkers of AKI: neutrophil gelatinase-associated lipocalin (NGAL) (I) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (II) in primary diagnostics of AKI. The thesis also investigated the risk factors for AKI development after severe burn injury and factors affecting the outcome (III), as well the need for long-term renal replacement therapy (RRT) after severe burn injury and possible association of burn injury and cause of death (COD) (IV).

Studies I and II enrolled 19 consecutive patients treated at Helsinki Burn Centre between March 2013 and September 2014. Plasma NGAL levels elevated over time in the majority of patients. Out of 19 patients, 17 showed elevated plasma NGAL levels (>150 ng/ml). Two patients showed high NGAL levels (>600ng/ml) without AKI. The area under the curve (AUC) was 0.62 in predicting AKI during the first week after a burn injury, whereas serum creatinine (SCr) and cystatin C (CysC) showed notably better diagnostic accuracy. A multivariable regression model showed that the NT-proBNP was correlated with the volume of infused fluids and age but found a negative correlation between the body mass index (BMI) and NT-proBNP levels. NT-proBNP increased over time in all patients. The variation between patients was substantial, and even more variation was observed in patients who developed AKI. No association between AKI and high NT-proBNP was discovered.

Study III found that 27.3% of patients developed AKI during the intensive care unit (ICU) stay, defined by an absolute SCr value of at least 120 µmol/l (1.4 mg/dl). 11.2% required RRT, and 19.8% of patients succumbed during their hospital stay. AKI patients showed 52.9% mortality compared to 7.4% of non-AKI patients. Age, TBSA%, sepsis and rhabdomyolysis were independent risk factors for AKI. The RRT had no effect on the significantly reduced mortality in AKI patients. AKI was associated with increased mortality, even in minor burns, and mortality increased substantially in major burns. The prognosis of major burns was relatively good

without AKI, though the majority of patients developed AKI in major burns (>50% burned TBSA). Age, TBSA%, sepsis and rhabdomyolysis were independent risk factors for AKI. Age, TBSA% and AKI were risk factors for death during an ICU stay. AKI substantially increased the risk of death (OR of 5.97, 95% CI 2.2-16.2).

Study IV included 68 burn patients who had received RRT in the Helsinki Burn Centre between November 1988 and December 2015. 52.9% of patients succumbed during their hospital stay, and 32 discharged patients remained for follow-up. The need for RRT subsided before discharge in 81.3% of survivors. 6.3% of survivors needed RRT for over three months. Two patients received RRT constantly for a total of 10.5 and 17 months, respectively. The need for RRT subsided over time in both cases. 35.7% of deaths occurred because of burns, 7.1% because of kidney failure and 57.1% of deaths occurred for any other reason. One patient developed chronic kidney disease (CKD) and succumbed during follow-up. The study showed CKD as a rare event after burn injury and RRT. It remains possible, however, that a prior burn injury may potentially enhance future development of AKI due to other reasons.

TIIVISTELMÄ

Palovamma on yksi vakavimpia tapaturmia, jolle on ominaista suora kudostuho ja sen käynnistämä yleinen tulehdusreaktio ja välittäjäaineiden aiheuttama elimistön tasapainon järkkyminen. Akuutti munuaisvaurio on yleinen vaikeiden palovammojen seuraus ja se lisää tuntuvasti kuolleisuutta. Korkea ikä, palovamman laajuus, hengitystiepalovamma, verenmyrkytys ja munuaistoksisten antibioottien käyttö ovat munuaisvaurion tunnettuja riskitekijöitä. Varhainen akuutti munuaisvaurio syntyy useimmiten verenkiertovajauksesta johtuvasta munuaisten riittämättömästä hapensaannista tai rabdomyolyysistä, kun taas myöhäinen akuutti munuaisvaurio on usein osana monielinvauriota, jolle on ominaista etenevä häiriötila veren hyytymisessä, keuhkojen hapetuskyvyssä ja munuaisten toiminnassa ja tila on usein vaikeasti hallittavissa. Tämän tutkimuksen tarkoituksena oli selvittää uusien akuutin munuaisvaurion merkkiaineiden, neutrofiilien gelatinaasiin assosioituvan lipokaliinin (NGAL) (I) ja N-terminaalisen B-tyypin pro-natriureettisen peptidin (NT-proBNP) (II) osuvuutta varhaisdiagnostiikassa. Tutkimus selvitti myös vakavan palovamman aiheuttaman munuaisvaurion riskitekijöitä ja potilaan ennusteeseen vaikuttavia tekijöitä (III). Lisäksi selvitettiin keinomunuaishoidon tarvetta pitkäaikaisesti potilailla, jotka ovat saaneet keinomunuaishoitoa tehohoidon aikana sekä näiden potilaiden kuolinsyyn yhteyttä munuaisvaurioon (IV).

Tutkimuksissa I ja II tutkimusaineiston muodostivat 19 prospektiivista HYKS Palovammakeskuksessa hoidettua tehopotilasta maaliskuun 2013 ja syyskuun 2014 välisenä aikana. 17:llä potilaalla 19:sta plasman NGAL ylitti suositellun alakatkaisupisteen (>150ng/ml) ensimmäisen viikon aikana. Kahdella potilaalla mitattiin hyvin korkeita arvoja (>600ng/ml) ilman merkkejä akuutista munuaisvauriosta. NGAL sai arvon 0.62 ROC-menetelmällä määritettynä akuutin munuaisvaurion diagnostiikassa ensimmäisen viikon aikana, kun taas seerumin kreatiniini ja -kystatiini C saavuttivat huomattavasti paremman tarkkuuden. NT-proBNP korreloi positiivisesti monimuuttujamallissa potilaiden saamaan kumulatiiviseen nestemäärään, korkean ikään ja negatiivisesti painoindeksiin. NT-proBNP nousi kaikilla potilailla ensimmäisen viikon aikana. Huomattavia yksilöllisiä eroja havaittiin potilailla, jotka kehittivät akuutin munuaisvaurion alkuvaiheessa ja heillä vaihtelu oli kaikkien suurinta. Yhteyttä akuutin munuaisvaurion ja NT-proBNP:n pitoisuuksien välille ei pystytty osoittamaan.

Tutkimuksessa III 27.3% potilaista sai akuutin munuaisvaurion (määriteltynä absoluuttisesti: seerumin kreatiniini >120 µmol/l (1.4 mg/dl)). 11.2% potilaista sai keinomunuaishoitoa,19.8% potilaista menehtyi hoitojakson aikana. 52.9% akuutin

munuaisvaurion saaneista potilaista menehtyi ja vain 7.4% niistä, jotka eivät saaneet munuaisvauriota.
Korkea ikä, palovamman laajuus, rabdomyolyysi ja sepsis olivat akuutin munuaisvaurion riskitekijöitä. Ikä, palovamman laajuus ja akuutti munuaisvaurio olivat kuoleman itsenäisiä riskitekijöitä, akuutti munuaisvaurio oli yksittäisenä tekijänä merkittävä, vetosuhteella 5.97 (95% luottamusväli: 2.2-16.2).
Keinomunuaishoitoa saaneilla kuolleisuus ei eronnut merkitsevästi muista munuaisten vajaatoimintapotilaista. Akuutti munuaisvaurio nosti kuolleisuutta jopa pienissä palovammoissa. Toisaalta laajassakin palovammassa ennuste oli suhteellisen hyvä, mikäli potilaalla ei ollut munuaisvauriota. Laajoissa palovammoissa tosin valtaosa potilaista saa akuutin munuaisvaurion.

Tutkimukseen IV kerättiin 68 potilasta, jotka ovat saaneet keinomunuaishoitoa marraskuun 1988 ja joulukuun 2015 välisenä aika HYKS Palovammakeskuksessa. 52.9% potilasta menehtyi hoitojakson aikana ja seurantaan jäi 32 potilasta, jotka kotiutuivat palovamman hoitojaksolta. 81.3 prosentilla oma munuaistoiminta palautui ennen kotiutusta. 6.3% seurantaan jääneistä saivat munuaiskorvaushoitoa yli 3kk:n ajan. Nämä potilaat (2kpl) saivat munuaiskorvaushoitoa jatkuvasti 10,5 ja 17kk ennen kuin molempien munuaistoiminta palautui. Palovamma oli kuolinsyy 35.7 prosentilla, krooninen munuaisten vajaatoiminta 7.1 prosentilla ja 57.1 prosentilla kuolinsyy oli jokin muu. Yhdelle potilaalle kehittyi krooninen munuaisten vajaatoiminta seuranta-aikana, mikä oli myös potilaan kuolinsyy. Tutkimus ei havainnut, että, krooninen munuaisten vajaatoiminta olisi yleinen ilmiö vaikean palovamman jäljiltä, mutta sellaisen kehittyminen on mahdollista.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Rakkolainen I and Vuola J. **Plasma NGAL predicts early acute kidney injury no earlier than s-creatinine or cystatin C in severely burned patients.** *Burns 42.2 (2016): 322-328*.

II. Rakkolainen I, Elmasry M, Steinvall I and Vuola J. **Plasma N-terminal brain natriuretic peptide one week after burn injury.** *Journal of Burn Care & Research*, 2018 vol. 39 (5) pp. 805-810.

III. Rakkolainen I, Lindbohm JV and Vuola J. **Factors associated to acute kidney injury in Helsinki Burn Centre in 2006-2015** *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine (2018) 26:105.*

IV. Rakkolainen I, Mustonen KM and Vuola J. **Long term outcome after renal replacement therapy in severe burns** (submitted).

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ABBREVIATIONS

ABA	American Burn Association
ABSI	Abbreviated Burn Severity Index
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ANOVA	Analysis of variance
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
AUC	Area under the curve
BE	Base excess
BMI	Body mass index
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
CCr	Creatinine clearance rate
CK	Creatinine kinase
CKD	Chronic kidney disease
COD	Cause of death
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CysC	Cystatin C
CVVH	Continuous veno-venous hemofiltration
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ESRD	End-stage renal disease
FFP	Fresh frozen plasma
FRKD	Finnish Registry for Kidney Diseases
GFR	Glomerular filtration rate
HES	Hydroxyethyl starch
HF	Hemofiltration
HD	Hemodialysis
HDF	Hemodiafiltration
HUH	Helsinki University Hospital
ICD	International Classification of Diseases
ICU	Intensive care unit
IHD	Intermittent hemodialysis
ITN	Ischemic tubular necrosis
KDIGO	Kidney disease improving global outcomes
LD_{50}	Median lethal dose (50% likelihood of death)

LD_{100}	100 percent lethal dose (100% likelihood of death)
MB	Myoglobin
MAP	Mean arterial pressure
MODS	Multiple organ dysfunction score
MOF	Multiple organ failure
NT-proBNP	N-terminal pro-brain natriuretic peptide
NGAL	Neutrophil gelatinase-associated lipocalin
NSAID	Nonsteroidal anti-inflammatory drug
POC	Point-of-care
RIFLE	Risk-injury-failure-loss-end stage renal disease
RL	Ringer's lactate
ROC	Receiver operating characteristic
RRT	Renal replacement therapy
SCr	Serum creatinine
SD	Standard deviation
SLED	Sustained low-efficiency dialysis
SOFA	Sequential organ failure assessment
TBSA	Total body surface area
UO	Urine output
WHO	World Health Organization

1. INTRODUCTION

Tens of thousands of people are estimated to be exposed to burns every year in Finland. The vast majority of burns heal with simple treatments without health care interventions. Around 50 people annually require intensive care unit (ICU)-level treatment for a major burn injury (Vaikeat palovammat 2019). Elderly patients and those with pre-existing comorbidities are at greater risk for unfavorable outcome (Nitzschke et al. 2017; Pompermaier, Steinvall, Fredrikson, et al. 2017).

The risk of death increases in major burns, especially with co-existing inhalation injury (Wu et al. 2016). Overall, major burn injuries are connected with remarkable mortality and adverse outcomes, such as acute kidney injury (AKI). Around 30-45 percent of severely burned patients encounter AKI during their hospital stay. The exact proportion varies depending on the definition for AKI and on the study material.

AKI increases significantly the probability of death, prolongs the ICU stay time and increases the economic burden for society. Early-onset AKI is encountered within days after the injury when caused by the lack of kidney perfusion due to insufficient circulation. Late-onset AKI is associated with a prolonged ICU stay, the administration of nephrotoxic antibiotics and as a part of multiple organ failure (MOF), which is a severe sequela of prolonged ICU stay (Holm et al. 1999).

Fluid resuscitation is a way to maintain sufficient perfusion to vital organs at the early stage of burn treatment. However, administration of excessive amounts of fluids may lead to complications, such as increased intra-abdominal pressure, extremity swelling, compartment syndrome, pulmonary oedema and deepening of the burn injury (Mason et al. 2016).

Kidneys may be protected from hypoperfusion by fluid resuscitation. Also, harmful medications can be discontinued, but complications can only be minimized in progressive AKI with renal replacement therapy (RRT) that removes excess fluid, corrects electrolytes imbalances and removes toxic metabolites.

The AKI diagnosis is mainly based on urine output (UO) and serum creatinine (SCr). SCr rises in the blood after a decrease in the glomerular filtration rate (GFR); however, it poorly reflects the rapid alterations of GFR, although creatinine is a kidney-specific substance (Nguyen & Devarajan 2008). Many biomarkers have been studied in AKI diagnostics, but most of them have failed to reach an acceptable diagnostic accuracy and kidney specificity to reach widespread use.

The ideal biomarker for AKI should be cost effective, easy and fast

to measure, be highly accurate and kidney specific. Early AKI diagnostics would possibly help to direct appropriate treatment efforts to avoid loss of kidney function. However, it must be noted that no clear evidence exists so far that interventions (such as early initiation of RRT) would improve the outcome.

Only scarce data exist about long-term kidney function impairment after AKI in severe burns. Current data from AKI patients hospitalized for various reasons suggest that the risk for chronic kidney disease (CKD) is increased even after complete recovery of kidney function and normalization of SCr (Chawla & P. L. Kimmel 2012; Jones et al. 2012). For burns, a few trials have suggested that burn-associated AKI increased the risk for future CKD development (Thalji et al. 2017; Helanterä et al. 2016).

Many scoring metrics have been created to evaluate the chance of survival at the beginning of ICU treatment. Many of these, such as the Baux and modified Baux score, account for the patient's age and burned total body surface area (TBSA%) and form an estimate of the final outcome. The Abbreviated Burn Severity Index (ABSI) score accounts also for sex, inhalation injury and medical history. These formulas were reasonably accurate when they were created, but due to today’s advanced medical treatment and improved knowledge of burn care, these formulas tend to be too pessimistic for the most severely injured patients. These formulas still have a fair prognostic value; however, as long as we lack effective therapies for AKI, the prognosis for AKI patients remains unsatisfactory.

This thesis investigated diagnostics of AKI, risk factors for AKI and its influence on prognosis in the burn population.

2. REVIEW OF LITERATURE

2.1 Thermal injury

Skin is the largest organ of the human body. The average surface area of an adult is 1.5-2 square meters. The skin acts as a barrier to protect the body from heat, cold, water loss and mechanical stress. The skin also acts as a protective barrier against pathogens and regulates the body's temperature by isolating heat and removing excess heat by sweating. The skin plays an important sensory role in sensing pain, vibration and temperature variations.

Thermal injury, such as a burn injury or frostbite, is tissue damage caused by excessive heat or cold. Burn injury is tissue damage caused by air, fluid, electrical current, radiation or a corrosive substance. Jackson presented three different areas in 1953 that can be distinguished at the burn site (Jackson 1953). The zone of coagulation (A) is the most central part of the injury where all the tissue is irreversibly damaged. It is surrounded by the zone of stasis (B), where some tissue is still vital. The outermost part is called the zone of hyperaemia (C)

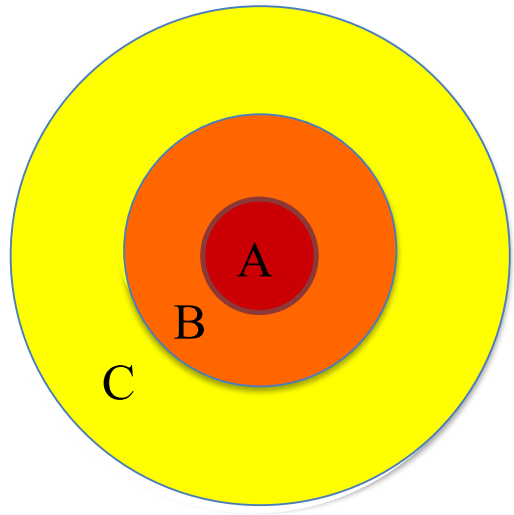


Figure 1 Jackson's burn model

where inflammation is present (Figure 1). The zone of coagulation is necrotic and thus does not heal. The zone of stasis is at risk of developing necrosis if adequate fluid resuscitation is not performed to ensure sufficient perfusion on the site.

Thermal injury is classified by the depth of the injury. The injury deepens within a few days of its occurrence and, in some cases, the evaluation of the final burn depth is postponed. A first-degree burn is isolated in the epidermis and heals conservatively without the need for health-care services. The most typical causes for a first-degree burn are sun burns and minor scald burns. Second-degree burn extends to the dermis. It often causes swelling, pain and blistering and the risk of infection

Figure 2 3rd degree contact injury from sauna stove.
From picture archive of Helsinki Burn Centre.

is increased. Superficial second-degree burns (classified also as IIa) heal conservatively in two weeks. Deeper second-degree burns (classified as IIb) need a longer time to heal and increase the risk of excessive scarring and infection. Skin grafting is needed to reach a good functional result and to avoid scarring and infection.

Third-degree burns (Figure 2) reach the subcutis and will not heal without surgical excision and skin grafting, except in very small injuries. Capillary reaction is absent, and the injury is often painless due to destruction of free nerve endings. The most extensive third-degree burns reach the muscle layer and even bone (sometimes referred as a fourth-degree burn).

2.2 Epidemiology of burn injuries

Large burn injury is one of the most severe injuries and accounts for a great economic burden on society (Ahn & Maitz 2012). Most of the total costs are from the primary ICU care. (Latifi et al. 2017). Total costs of an extensive burn injury in Finland may

rise up to more than 500.000 EUR per patient (Haikonen et al. 2016).

73% of burn injuries happen at home; the victim is male in 68 % of cases, and fire is the burn mechanism in 43 % of cases (American Burn Association 2015). At least 20,000 people are estimated to suffer from a burn injury requiring medical services annually in Finland. However, a vast majority of burn injuries are minor and are healed conservatively with no need for health- care services. Fewer than 1000 patients are hospitalized for burns annually in Finland, and roughly 50-60 of them require treatment in the ICU (Vaikeat palovammat 2019).

Severe burn injuries cause substantial changes in hemodynamics and tissue perfusion. Patients often need support in ventilation and circulation and also require potent pain management. Most of the burn injuries treated in the ICU are caused by flame in Finland. The proportion of fire-related burn injuries among all hospitalized burn patients was around one third in 2000-2009 in Finland (Tanttula et al. 2018). Fire-related burn deaths are slightly more common in Finland in comparison to other western countries. The incidence of fire-related death was estimated to be 2.0 per 100.000 inhabitants in Finland in 2009, whereas in New Zealand, for example, it was 0.8, in USA 1.0, in Sweden 1.3, in Denmark 1.3 and in Russia 9.8 (World Fire Statistics Centre 2011). The mortality rate of burn injuries has been reported lower in high-income countries than in low-income countries (Smith et al. 2016). Burn injury-related mortality has decreased over time, mainly due to specialized institutions established only for burn treatment (Burn units) (Akerlund et al. 2007). The first burn unit was launched in 1988 in Helsinki and later on in 1994 in Kuopio, eastern Finland. Treatment of all severe burns in Finland was centralized to one national institution, to Helsinki Burn Centre at Jorvi Hospital in Espoo in the beginning of 2016.

2.3 Pathophysiology of burn injury

Burn trauma increases vascular permeability by indirect and cytokine-mediated pathways. This so-called capillary leakage causes plasma transfer from vessels into tissues, which can be seen as excessive swelling on the burn site. Increased vascular permeability allows large oncotic molecules to transfer from vessels into tissues, which decreases colloid osmotic pressure in vessels and decreases circulating blood volume. Circulating blood volume is even decreased due to excessive evaporation of water from burned skin. An animal model conducted with rats suggested that burn trauma decreases interstitial pressure in tissues; in addition to capillary leakage, that enhances the movement of fluid from vessels into tissues (Imbition force)

(Lund et al. 1988). In conclusion, these mechanisms decrease perfusion to vital organs; this lack of blood volume is temporarily replaced by fluid resuscitation.

Burn injury not only affects blood vessels but also decreases cardiac output by systemic inflammation response syndrome and an increased number of oxygen-free radicals (Demling et al. 1978). Released catecholamines also increase peripheral vascular resistance for days after a burn injury (Crum et al. 1990).

2.4 Fluid resuscitation in severe burns

The Parkland formula (4ml/kg x TBSA%) was presented in 1968; since then, it has been the most used resuscitation formula among burn patients (Baxter & Shires 1968). Major burn injury causes fluid leakage into tissues by increasing vascular permeability. Significant amounts of fluids are also lost by increased evaporation from the burned skin (Friedl et al. 1989). The goal of successful fluid resuscitation is to replace this volume and secure sufficient perfusion to vital organs but not to over-resuscitate with its subsequent negative consequences. The evaluation of sufficient fluid resuscitation is mainly based on diuresis, blood pressure, tissue perfusion and the signs of over-resuscitation (Holm 2000). However, these parameters reflect more of the macro-circulation and not the sufficient perfusion of any specific organ, such as the kidneys, which are vulnerable to inadequate perfusion (Soussi & Legrand 2016). The Parkland formula is currently widely used, though some updates have been announced (Greenhalgh 2010). The need of resuscitation (4ml/kg x TBSA%) increases relatively more in large burns and in paediatric patients with smaller body mass (Cancio et al. 2004). A recently announced report observed that restrictive resuscitation is a risk for AKI development (Mason et al. 2016), but over-resuscitation may lead to compartment syndrome, extremity swelling, wound infections, pulmonary oedema and even MOF (Saffle 2016; Mason et al. 2016). Over-resuscitation may also deepen the burn wound itself.

Albumin and fresh frozen plasma (FFP) increase intravascular oncotic pressure and thus help to maintain sufficient intravascular volume (Cartotto & Greenhalgh 2016). The use of albumin in burn resuscitation currently is considered probably more beneficial than using only Ringer´s Lactate (RL) (Navickis et al. 2016). A recent meta-analysis with 140 patients showed that using albumin in burn resuscitation provided neither an advantage nor disadvantage (Eljaiek et al. 2017). Another study of 42 burn

patients found that fluid resuscitation with albumin did not decrease multiple organ dysfunction score (MODS) in the first two weeks after arrival (Cooper et al. 2006). Administration of albumin to 159 burn patients within the first 24 hours decreased mortality and need for vasopressors during ICU stay (Park et al. 2012). Resuscitation of burn patients by hypertonic saline solution has been justified by less administration, therefore, potentially reducing the risk for volume complications. In a small study of 36 severely burned patients, hypertonic saline groups compared with RL groups observed a reduced risk for secondary abdominal compartment syndrome (Oda et al. 2006). However, sufficient evidence to support the use of hypertonic saline in fluid resuscitation does not exist. Use of hypertonic saline in a wider spectrum has not reduced mortality in critically ill patients (Martin et al. 2018).

Hydroxyethyl starch (HES) is a starch derivative that increases intravascular volume with less administration compared to RL. Since being introduced in the 1960s, it has been connected with increased risk of AKI and death in critically ill patients (Gattas et al. 2013). European Medicines Agency (EMA) discouraged the use of HES-infusions among the burn population in 2013. In general, these infusions should be preserved only to replace blood loss when other means are insufficient (European Medicines Agency 2013). These instructions were based on studies that failed to mention whether they included patients with severe burns (> 10-20% burned TBSA) (Perner et al. 2012; Guidet et al. 2012; Myburgh et al. 2012; Annane et al. 2013; Brunkhorst et al. 2008). Earlier studies on burn population on pentastarch and albumin demonstrated a more favorable effect on hemodynamic parameters when administered 24h after injury (Waxman et al. 1989). Resuscitation with RL combined with HES in two modern studies including only patients with burned TBSA >15-20% showed that using HES did not increase risk of AKI or death, though they also did not support the use of HES as beneficial (Béchir et al. 2013; Béchir et al. 2010).

2.5 Diagnosis of AKI

The diagnosis of AKI has been based on SCr and UO for a long period of time. SCr is a waste product of muscle metabolism and is excreted from the circulation by the kidneys. SCr is cost effective (only a few EUR per measurement), kidney specific and readily available in hospitals and health care units. SCr's weakness is its inability to react in rapid changes of kidney function, and more than 50 percent of kidney function must be lost before plasma elevation can be measured. The SCr baseline is dependent on age, sex, muscle mass and ethnic background, which set a

challenge to evaluate the GFR in individual patients (Nguyen & Devarajan 2008). Increases in SCr after repeated measurements are more informative when evaluating developing AKI (Lameire & Hoste 2004). Some physiological conditions, such as sarcopenia, hepatic insufficiency, increased fluid volume and sepsis, decrease SCr levels, whereas trauma, fever and immobilisation increase the SCr levels (Clark et al. 2017). The severity of AKI is generally classified by Risk-Injury-Loss-End stage renal disease (RIFLE), Acute Kidney Injury Network (AKIN) or Kidney Diseases Improving Global Outcomes (KDIGO) criteria (Table 1). All of them include SCr and UO as diagnostic criteria. RIFLE also includes decreases in GFR. Classification in recent papers of AKI in severe burns has been based mainly on either AKIN or RIFLE criteria (Table 1). All classifications have similar criteria and time limits for worsening of diuresis. However, these classifications have essential differences: RIFLE classification considers only a percentage-based SCr rise at the lowest gradings (Risk&Injury), whereas KDIGO and AKIN classifications also allow grading based on an absolute increase in SCr. Reaching a significant percentage-based rise is more difficult in situations where baseline SCr is elevated (dehydration, CKD, rapid AKI). RIFLE classification sets a one-week time limit for deterioration, whereas AKIN classification limits the time period for only 48 hours, which rules out a slowly developing worsening of kidney function. It must be noted that even small increments in SCr in rapid sequence increase the risk of death.

Table 1 AKIN, RIFLE and KDIGO classification for AKI

RIFLE (Bellomo et al. 2004)		
Risk	SCr increased 1.5-2-fold from baseline OR GFR decreased > 25%	< 0,5 ml/kg x h > 6h
Injury	SCr increased 2-3-fold from baseline OR GFR decreased > 50%	< 0,5 ml/kg x h > 12h
Failure	SCr increased > 3-fold from baseline OR GFR decreased > 75% OR SCr > 4 mg/dL (354 µmol/L) with an acute rise 0.5 mg/dL (44 µmol/L)	< 0,3 ml/kg x h > 24h OR anuria > 12h
Loss	Complete loss of kidney function > 4 weeks (Requiring RRT)	
End-stage renal disease	Complete loss of kidney function > 3 months (Requiring RRT)	
AKIN (Mehta et al. 2007)		
AKIN 1	Increase in serum creatinine at least 0.3 mg/dL (26.4 µmol/L) or increase at least to 150-200% (1.5- to 2-fold) from baseline.	Less than 0.5 mg/kg per hour for more than 6 hours.
AKIN 2	Increase in serum creatinine more than 200-300% (2- to 3-fold) from baseline.	Less than 0.5 mg/kg per hour for more than 12 hours.
AKIN 3	Increase in serum creatinine more than 300% (> 3-fold) from baseline or serum creatinine at least 4.0 mg/dL (354 µmol/L) with an acute increase at least 0.5 mg/dL (44 µmol/L) or need for RRT	Less than 0.3 mg/kg per hour for more than 24 hours or anuria for 12 hours or need for RRT.
KDIGO (Kellum et al. 2012)		
KDIGO 1	SCr increased 1.5-1.9-fold from baseline within 7 days OR 0.3 mg/dL (26.4 µmol/L) increase in 48h	< 0,5 ml/kg x h > 6h
KDIGO 2	SCr increased 2-2.9-fold from baseline	< 0,5 ml/kg x h > 12h
KDIGO 3	SCr increased > 3-fold from baseline OR SCr > 4 mg/dL (354 µmol/L) OR need for RRT	< 0,3 ml/kg x h > 24h OR anuria > 12h

(Gruberg et al. 2000; Lassnigg et al. 2004; Levy et al. 2005; Praught & Shlipak 2005). KDIGO classification was created to combine the strengths of RIFLE and AKIN classifications. It allows diagnosis of mild AKI by an acute rise in SCr within 48h or by a percentage-based rise within one week.

According to a systematic review of a heterogenous study population of 71000 patients, the RIFLE classification accurately predicted that mortality and the risk of death increased with a higher grading of AKI (Ricci et al. 2008). A multicenter study of over 16000 ICU patients concluded RIFLE was superior to AKIN classification in predicting hospital mortality based on kidney function deterioration within 48h from admission (Joannidis et al. 2009). Another study of 1973 burn patients demonstrated that AKIN classification was superior to RIFLE classification in predicting AKI (Chung et al. 2012). KDIGO-criteria are nowadays the golden standard in AKI definition.

Several biomarkers other than SCr have been investigated to enhance the accuracy of AKI diagnostics, but many of them have failed to make a breakthrough into clinical use, mostly due to poor specificity to AKI and a lack of sufficient evidence (Zhang et al.

2019). Novel biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), N-terminal pro-brain natriuretic peptide (NT-proBNP) and cystatin C (CysC), are discussed further.

2.6 Kidneys and aetiology of acute kidney injury

Humans have two kidneys (Figure 3) that are located on both sides of the vertebral column at the level between the 12th thoracic and 3rd lumbar vertebrae in the retroperitoneal space and are surrounded by fat tissue. Each kidney has a blood supply via a single renal artery and vein, and the produced urine is collected by a single ureter leading into the bladder. Kidneys have an important function as regulators of the acid-base balance, extracellular fluid balance, and blood pressure. They remove toxic wastes such as urea, reabsorb minerals and produce erythropoietin. Kidneys control fluid balance by regulating the amount of secreted urine and its concentration.

AKI (earlier referred to as acute renal failure (ARF)) is a loss of kidney function happening in a short period of time. At an early stage this can be noticed as alterations in electrolyte levels, mild fluid accumulation with peripheral oedema and a decreased amount of secreted urine. In severe AKI this is followed by increased concentrations of potassium and urea in the blood and total anuria and fluid accumulation into the lungs or peritoneal cavity. The aetiology leading to AKI can be distinguished as prerenal, renal or postrenal causes. Prerenal AKI is caused by insufficient blood and oxygen supply to the kidneys due to obstruction of the renal artery or decreased mean arterial pressure (MAP) and insufficient perfusion of the kidneys. Renal causes account for kidney diseases and destruction of nephrons. This can be caused by hypertension, diabetes mellitus, glomerulonephritis, or some vasculitis. Various medicines, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antihypertensive drugs, diuretics and imaging contrasts, are harmful, as is myoglobin (MB) released from destroyed myocytes. Postrenal causes include urological situations in which drainage of urine via ureters is interrupted, for example, by kidney stones or increased intra-abdominal pressure or a tumor. AKI develops after a severe burn injury via prerenal or renal causes. A postrenal cause is plausible due to excessive fluid resuscitation causing obstruction of ureters via increased intra-abdominal pressure, but the burn injury itself is not a direct factor for postrenal AKI. Sometimes AKI turns into a long-term impairment of kidneys; CKD means the worsening of kidney function for at least three months. ESRD means the permanent loss of kidney function, requiring RRT.

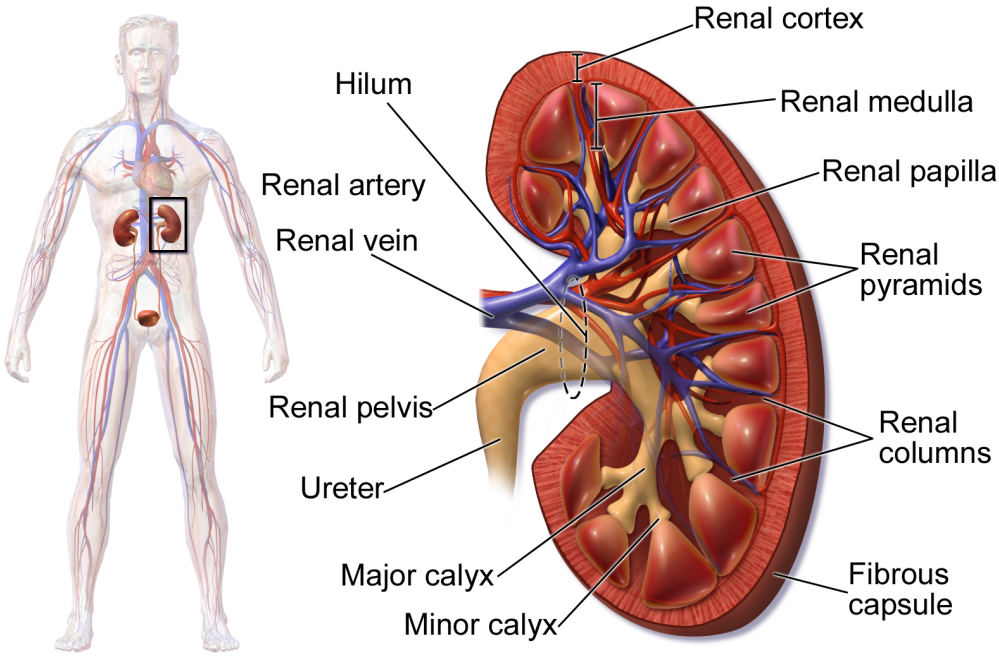


Figure 3 Anatomy of human kidney

https://en.wikipedia.org/wiki/Kidney#/media/File:Blausen_0592_KidneyAnatomy_0

2.7 Acute kidney injury in burns

AKI is a common complication after an extensive burn injury. The likelihood of AKI increases in larger burn injuries. Other known risk factors are high age, simultaneous inhalation injury, flame burn, the burn injury's thickness, sepsis and rhabdomyolysis (Wu et al. 2016; Stewart et al. 2013). It must be noted that AKI is not uncommon even in small burn injuries (TBSA < 20%) (L. A. Kimmel et al. 2018). AKI that occurs within five days postburn is classified as "early," after which it is classified as "late" (Holm et al. 1999). Some studies however have classified AKI as "early," when encountered within 14 days postburn (Chung et al. 2009). Early AKI in burns is primarily caused by insufficient perfusion of kidneys due to a circulation deficit, cytokine-mediated cardiac dysfunction, hypovolemia, ongoing inflammatory response or breakup of proteins; these lead to ITN (Vaidya et al. 2008; D. M. Davies et al. 1979; Aikawa et al. 1990; Mukherjee et al. 1987). Cytokines that are released after injury cause "capillary leakage," which increases plasma transfer to tissues and thereby decreases circulating blood volume (Demling 2005). Early AKI is common especially in rhabdomyolysis and hot air sauna-related burn injuries when

dehydration is present (Mustonen & Vuola 2008). Rhabdomyolysis is caused by damage in muscle tissue, which releases MB into the circulation. Released MB causes direct proximal tubule injury after several chemical reactions, and it may even obstruct the distal tubule by casts that are formatted (Bosch et al. 2009; Petejova & Martinek 2014). Rhabdomyolysis is diagnosed by an increase in serum creatinine kinase (CK), and a concentration of 10.000 U/l has been used as a cut-off value in clinical practice, though rhabdomyolysis has also been described with lower CK levels (de Meijer et al. 2003; Ward 1988). Myoglobinuria often follows rhabdomyolysis. MB is a hemoglobin-like protein that supplies oxygen in skeletal muscles, especially under enormous physical stress. MB is released from muscle cells along with a multiphase cascade following this, causing direct proximal tubule injury and obstruction in distal tubules, causing AKI (Bosch et al. 2009). In rhabdomyolysis, MB usually rises faster than plasma CK in blood and is therefore preferred in diagnostics.

Late AKI may follow nephrotoxic drug administration and is often part of MOF or sepsis, which are adverse outcomes of a prolonged ICU stay (Holm et al. 1999). Literature shows contradictory results both in early and late AKI's contribution to the outcome (Witkowski et al. 2016; Schneider et al. 2012). The differences in outcomes are likely explained by differences in the study populations and the definition of AKI that is used. Based on the aetiology of AKI, early AKI can be treated with circulation supportive methods, like fluid resuscitation and vasoactive drugs. RRT may be initiated in severe AKI to remove harmful substances like ammonium and urea from the blood. Whereas developing early AKI may subside rapidly with fluid resuscitation, late AKI is often associated with sepsis and as a part of MOF, a poorly manageable state (Steinvall et al. 2008). Early studies in the 1990s concluded that early AKI is associated with better outcomes compared to late AKI (Davies:1994ut; Aikawa et al. 1990). Since then, several studies have contradicted these observations (Witkowski et al. 2016; Holm et al. 1999; Mustonen & Vuola 2008). It must be emphasized that all these studies use different definitions for AKI, for early and late onset AKI, as well as using heterogenous patient selection and exclusion criteria, which makes the comparison of these studies impossible.

Table 2 Incidence and mortality of AKI in burned patients on previous studies [1)] Year(s) when data collected or published (pub.)

Authors	Years[1]	Number of patients	Incidence of AKI (%)	Incidence of RRT (%)	AKI Mortality (%)	Inclusion criteria	Criteria for AKI
Cason JS	1953-1956	3690	1.3		100		
Evans AJ	1953-1966	602	0		0	Pediatric burn patients	
Cameron and Miller-Jones	1953-1966	720	3.1		95.5	Pediatric burn patients	Blood urea > 1mg/ml
Vertel and Knochel	1960-1966	1050	2.3		87.5	All patients admitted	BUN > 40mg/dl or nonprotein nitrogen > 50 mg/dl
Cameron	1967	110	20		95.5	Children, > 15% burned TBSA	Blood urea > 1 mg/ml
Davies et al	1958-1979	1064	2.6	2.4	85.7/88	All patients admitted	Need for RRT
Tweddell et al	1964-1983	91	4.4		100	Pediatric burn patients with hematuria	
Hubsher et al	1984-1985	5		100	80	Burn patients, need for RRT	
Planas et al	1982 (pub.)	29	38			2-3 dg. burn, >30% TBSA	
Schiavon et al	1988 (pub.)	20	20		100		SCr > 133 µmol/l
Aikawa et al	1990 (pub.)	158	10.8		88.2		Clearance < 50ml/min or BUN > 50mg/dl or SCr > 175µmol/L
Saffle et al	1987-1990	529	9.5		46	All patients, length of stay > 72h in ICU	Thermal Injury Organ Failure Score (moderate: SCr > 221 µmol/L)
Davies et al	1994 (pub.)	18 burn units	< 1%		80	A questionnaire study	Need for RRT
Schreidan et al	1989-1994	56	68	21	100	Succumbed patients	Serum BUN > 100 or SCr > 3.5 or UO < 500ml/24h
Leblanc et al	1987-1994	970		1.6	81.3	All patients admitted	Fluid retention or pulmonary oedema, or S-Urea > 35 µmol/L
Jeschke et al	1966-1997	5000	1.2	0.7	73	Children, all patients admitted	UO < 0,5ml/kg x h >36h or Serum urea nitrogen/creatinine ratio < 20 or SCr > 177µmol/L or need for RRT
O'Keefe et al	1989-1998	4927	1.9			All patients admitted	
Holm et al	1994-1998	328	14.6	14.6	85.4	Patients with deep burn, TBSA > 10%	Need for RRT
Tremblay et al	1995-1998	353	3.4	3.4	50	All patients admitted	Need for RRT
Chrysopoulo et al	1981-1998	1404	5.4	4.8	88.2	Patients with TBSA burned > 30%, >10% 3 dg. burn	3 of these: UO < 350ml/36h, BUN/Cr < 20, SCr > 177µmol, need for RRT
Barrow et al	1982-1999	133	30.1			Children, >50% TBSA	2 of these: UO< 0.4ml/kg x h >36h, BUN >50 mg/dl, U-Cr/S-Cr >20, SCr > 2mg/dL

Table 2 continues

Cumming et al	1998-1999	85	3.5			Patients with > 20% TBSA	MODS (3-4, SCr > 350 µmol)
Spies et al	1996-2000	33	15.2		80	Children, TBSA >80% or >70% full-thickness	SCr > 20mg/L
Kim et al	2000	147	19	2	100	Patients with > 30% TBSA 2-3 dg.	SCr > 177 µmol/L
Cooper et al	1999-2001	42	14.3			Patients with > 20% TBSA	MODS (3-4, SCr > 350 µmol/L)
Mustonen and Vuola	1988-2001	238	39.1	13.4	44.1	All patients admitted ICU	SCr ≥ 120 µmol/L
Sun et al	1997-2003	6		100	83.3	Burn patients >30% TBSA, requiring RRT	
Coca et al	1998-2003	304	27	3.6	28	Patients with > 10% TBSA	RIFLE
Gudaviciene et al	2000-2003	138	10.1		85.7	Patients aged 16-80 with 10-80% burned TBSA%	
Garner et al	1994-2004	3118		1.4	66	All patients admitted	
Steinvall et al	1997-2005	127	24	3.1	35.5	Patients with > 20% TBSA	RIFLE
Mariano et al	2003-2005	29	65.5	51.7	52.6	Burn patients with septic shock	RIFLE
Lopes et al	2004-2005	126	36		47	All patients admitted	RIFLE
Kuo et al	2004-2006	145	35.9		50.9	Patients aged >18 years	KDIGO
Mosier et al	2008 (pub.)	221	28.1	11.3	35.5	Patients with > 20% TBSA, aged >18 years	RIFLE
Chung et al	2003-2008	1973	33.2	4.1	21	Patients with age >18 years	AKIN
Stewart et al	2003-2008	692	23.8	5.9	24.2	Burned military casualties	RIFLE
Schneider et al	2006-2008	221	47.1	11.3	35.6	Patients aged >18, >20% TBSA	RIFLE
Palmieri et al	2006-2008	123	45.5		8.9	Children with > 10% TBSA	RIFLE
Sabry et al	2009 (pub.)	40	22.5	10	22.2	Patients with 20-70% TBSA	SCr >2mg/dL or BUN >25mg/dL
Hu et al	2006-2010	396	38.1	4	28.5	Patients with > 30% TBSA, Age 18-75	RIFLE
Palmieri et al	2010 (pub.)	60	53.3		34.4	Patients with > 20% TBSA	RIFLE
Damkat-Thomas et al	2011 (pub.)	41	41	12.2	35	All patients admitted	RIFLE
Clemens et al	2003-2011	830	48.2		43	All patients admitted ICU, mechanical ventilation	KDIGO
Sánchez- Sánchez et al	2008-2011	165	19.4	9.1	50	TBSA 15-85%, Age 16-80	RIFLE
Noshad	2008-2011	100	76		38.2	All patients admitted	RIFLE
Yavuz et al	2009-2011	22	27.3			Paediatric burn patients, >10% TBSA	RIFLE

Table 2 continues

Estrada et al	2002-2012	146	4.8		87.5	TBSA >25%, (>20% in >40-yr, >10% 3rd burns, aged >14 yr.)	
Queiroz et al	2010-2012	293	26.3	17.7		Patients aged >18	KDIGO
Hong et al	2011-2012	45	24.4	11.1	72.2	Patients aged >18, >20% TBSA	RIFLE
Yang et al	2011-2012	90	61.1	24.4	69.1	Patients aged >18, >20% TBSA	RIFLE
Ren et al	2013	95	11.2	5.3	36.4	Patients aged 15-65	KDIGO
Thalji et al	2009-2013	1476, register study	20.7		62.4	Patients with >20% TBSA	ICD-9 coding
Yim et al	2012-2013	97	41.2	23.5	52.5	Patients aged >18	AKIN
Witkowski et al	2012-2013	225	40	4	88	Patients with >30% TBSA	GFR < 60ml/min at admission or GFR decrease >75% from admission or UO <500ml/24h
Kym et al	2012-2013	85	56.5	25.9	64.6	Patients aged >18, >20% TBSA	RIFLE
Lavrentieva et al	2006-2014	64	57.8	28.1	62.2	Patients with septic shock, aged >18, >10% TBSA	KDIGO
Liang et al	2009-2014	59	39			Patients, TBSA >40% 2-3 dg	RIFLE
Kimmel et al	2010-2014	267	22.5		8.3	Patients, TBSA >10%	RIFLE
Howell et al	2015 (pub.)	15	46.7			Patients aged >18, >20% TBSA	RIFLE
Sen et al	2015 (pub.)	30	46.7	10		Patients aged >18, >20% TBSA, 2-3 dg.	RIFLE
Clark et al	2008-2015	1040	57.8	5.6	20.3	Burn > 18yrs patients admitted to ICU	AKIN, without diuresis criterion
Dépret et al	2012-2015	87	44.8	24.1	82	Patients aged >18, >20% TBSA	KDIGO
Chun et al	2014-2015	76	42.1	26.3	68.8	Patients aged >18, >20% TBSA	AKIN
Koniman et al	2008-2016	201	65.6	21.9	34.1	All patients admitted	SCr rise more than 26.5 µmol/L
Kim et al	2015-2016	84	41.7	21.4	82.9	Patients aged >18, >20% TBSA	AKIN
Chung et al	2018 (pub.)	170	94.1	100	50	RRT patients, >18 years	AKIN
Pooled studies							
Bruesselaers et al	1960-2009	34771, 57 studies	14.5 (median)		55.2		23 different definitions

Table 2 continues

Wu et al	2007-2016	3941, 18 studies	39.6	30.6	RIFLE

The first survivors from AKI caused by burn injury were reported in the early 1960s. Over time the prognosis has improved notably, though AKI still increases the risk of death. (Brusselaers et al. 2010). Table 2 shows studies conducted on burn patients, the incidence of AKI/RRT and the mortality of AKI patients. The variety of study populations and over 20 different definitions for AKI make it impossible to compare the studies with each other. Even more definitions for AKI have been presented during past decades (Brusselaers et al. 2010). In conclusion, even in the 21st century, AKI is a common complication after severe burn injury. Mortality has decreased over time but still remains at a level of tens of percents.

2.8 Treatment of AKI

No specific curative treatment exists for AKI. The goal of interventions is to secure a sufficient perfusion of the kidneys by fluid resuscitation and, if necessary, by administration of vasopressors, which increase MAP and/or cardiac output. Treating AKI by urine alkalinization with sodium bicarbonate or by administration of mannitol has been proposed, but studies have not supported this as beneficial (B. Yang et al. 2014; Brown et al. 2004). A low-dose dopamine infusion increased the creatinine clearance rate (CCr) in eight ICU patients, but the effect was lost within 48 hours, likely due to upregulation of dopamine receptors in kidney arteries (Ichai et al. 2000). Administration of a dopamine receptor agonist, fenoldopam, reduced the risk of RRT and mortality according to a meta-analysis consisting of 1290 heterogenous, critically ill ICU patients from 16 studies (Landoni et al. 2007). In a randomized multicenter study of 667 cardiac surgery patients, fenoldopam did not reduce mortality or need for RRT in the 30-day follow-up but caused more hypotension (Bove et al. 2014). In a retrospective study of severely burned patients, administration of fenoldopam increased UO, but the study did not provide evidence for reduced mortality or a decreased need for RRT (Simmons et al. 2010). Many trials are ongoing in which novel pharmacological agents are being investigated to learn if they could be helpful in preventing AKI (Benoit & Devarajan 2018).

RRT may be considered in the most severe AKI cases to manage life-threatening situations such as hyperkalemia or severe fluid accumulation. The modern RRT techniques were launched in the early 1960s (Scribner et al. 1960; Pendras et al. 1961). Table 2 shows that the need for RRT after AKI is notably rare when considering the incidence of AKI during the past decades. Techniques to perform RRT include hemodialysis

(HD), hemofiltration (HF) and hemodiafiltration (HDF) as intermittent or continuous. Sustained low-efficiency dialysis (SLED) is a modified dialysis technique in which the dialysis duration is extended up to 12 hours to improve hemodynamic tolerability.

No consensus exists about whether early initiation of RRT reduces mortality or if some RRT techniques are superior to others. Continuous renal replacement therapy (CRRT) is usually better tolerated in patients with labile hemodynamics. A retrospective cohort of 232 ICU patients compared SLED vs. CRRT in critically ill patients. It observed no significant difference in 30-day mortality (Kitchlu et al. 2015). In general ICU patients in a randomized prospective multi-center study on 1124 critically ill patients showed no reduced 90-day mortality when intensive dialysis therapy was compared to less-intensive therapy (RENAL Replacement Therapy Study Investigators et al. 2009). A recent single-center randomized study of 231 critically ill patients showed significantly reduced 90-day mortality in patients with early RRT initiation vs. delayed RRT initiation (Zarbock et al. 2016). Another multi-center randomized trial showed no difference in 60-day survival when accelerated RRT initiation was compared to a delayed strategy (Gaudry et al. 2016). Another study showed no difference in in-hospital mortality nor in 90-day mortality between accelerated vs. standard RRT initiation in 100 critically ill patients (Wald et al. 2015).

Protective evidence of RRT to reduce mortality among burn patients is minor. A small retrospective cohort of 28 burn patients who received continuous veno-venous hemofiltration (CVVH) showed a reduced risk of mortality compared to matched controls (Chung et al. 2009), as well as a retrospective study of 18 military casualties who underwent CRRT compared to matched controls (Chung et al. 2008). A randomized clinical trial investigated whether early RRT initiation improves the prognosis compared to standard care in burn patients suffering septic shock (ClinicalTrials.gov ID: NCT01213914). The study was terminated ahead of time due to slow enrollment. It concluded early RRT initiation to improve organ dysfunction; however, no difference in survival was noted (Chung et al. 2017).

2.9 Long term outcomes after AKI in severe burns

A systematic review comprising 13 studies showed that AKI increased the risk for CKD and end-stage renal disease (ESRD) after discharge in general hospitalized patients (Coca et al. 2012). However, evidence suggests that hospitalized patients with mild AKI whose kidney function recovers generally do not have an increased risk for ESRD (Choi et al. 2010), though

conflicting evidence has been proposed based on a Canadian study of 41327 patients with AKI (Wald et al. 2012).

There is only moderate evidence of long-term renal outcomes in severe burns after RRT. A few studies have reported that kidney function in most patients recovers before discharge (Soltani et al. 2009). An American multicenter study reported 21% of patients as being dependent on dialysis at the moment of discharge and 9% six months after discharge (Chung et al. 2018). The risk of ESRD after burn injury is rare, according to a Finnish register study. Around 0.1% of all burn patients treated as in- or outpatients between 1998-2012 in Finland suffered from ESRD after burn injury (43 patients). 88.4% of patients (38 patients) had diagnosed kidney disease before their burn injury. Researchers concluded that the burn injury might have been a plausible cause for ESRD in five out of 41179 patients but, unfortunately, further explanations were not given (Helanterä et al. 2016). Another American register study concluded that AKI was a risk factor for CKD and chronic RRT by multivariable regression analysis, adjusted with co-morbidities one year after injury (Thalji et al. 2017). However, recent evidence suggests that pre-existing chronic impaired kidney function before a burn injury is an individual risk factor for in-hospital mortality at 30 and 60-days since injury (Knowlin et al. 2018).

2.10 Novel biomarkers in AKI diagnostics

2.10.1 Cystatin C (CysC)

CysC was discovered in 1961 (Clausen 1961). It is a 13.4 kD-sized proteinase inhibitor found in every nucleated cell in the human body. CysC is normally filtered through glomeruli and reabsorbed in the proximal tubule. Decreases in GFR increase CysC concentrations in plasma, which can be measured. CysC concentrations are independent of age, sex, body and muscle mass, making it a more ideal biomarker for AKI due to less confounding factors affecting the values (Herget-Rosenthal et al. 2004). Plasma CysC has been evaluated as a fair biomarker for detecting AKI in general ICU patients (Ahlström et al. 2004; Herget-Rosenthal et al. 2004), after liver transplantation (Hei et al. 2008) in emergency department setting (Soto et al. 2010) and after cardiac surgery in adults (Haase-Fielitz et al. 2009; Haase, Bellomo, Devarajan, Ma, et al. 2009; Ristikankare et al. 2010) and children (Krawczeski et al. 2010; Zappitelli et al. 2011)

Controversial and limited evidence exists when using CysC for detecting AKI among burn population. Serum CysC has been evaluated in

two papers as superior to SCr with adult burn patients (Yim et al. 2015; X. Cai et al. 2012); however, recent studies have not been able to confirm it as superior to SCr (Kym et al. 2015; H. T. Yang et al. 2014)

2.10.2 Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a 25kD-sized molecule of the lipocalin family, that was discovered in human neutrophils in 1994 (Xu et al. 1994). NGAL was discovered thereafter in the epithelia of colon, trachea, kidney, stomach and lungs, where it is expressed in very low concentrations under normal conditions (Xu & Venge 2000). NGAL is found in three different isoforms: a 25kD monomer, a 45kD dimeric and a 135kD heterodimeric form. (Kjeldsen et al. 1993). Kidney tubule cells express the monomeric and dimeric form, whereas neutrophils only express the dimeric form (L. Cai et al. 2010). Elevated concentrations of NGAL have been discovered in patients with severe peritonitis (Axelsson et al. 1995), cystic fibrosis (Eichler et al. 1999), chronic obstructive pulmonary disease (Ekberg-Jansson et al. 2001), rheumatoid arthritis (Bläser et al. 1995) and also in professional swimmers constantly exposed to chlorinated water (Helenius et al. 1998). The diagnostic value of NGAL for kidney tubular injury was discovered in 2003 in mice (Mishra et al. 2003), and the first human study was conducted in 2005 (Mishra et al. 2005). The concentrations of NGAL rise rapidly in blood and urine in damaged kidney epithelium after ITN (Vaidya et al. 2008).

NGAL has been widely studied in AKI diagnostics in various study populations and settings. Plasma and urine NGAL were evaluated as good biomarkers in predicting contrast-induced AKI (K. Wang et al. 2016), AKI after cardiopulmonary bypass in adults and children (Moriyama et al. 2016; Parikh, Coca, et al. 2011; Parikh, Devarajan, et al. 2011) in an emergency department setting (Nickolas et al. 2008; Shapiro et al. 2010) and in the general ICU setting (Makris et al. 2009; Constantin et al. 2010). Urine NGAL has been evaluated as slightly more accurate than plasma NGAL in AKI diagnostics in various patient settings by a meta-analysis (Haase, Bellomo, Devarajan, Schlattmann, et al. 2009). A Finnish study, however, noticed urine NGAL to be a poor predictor of AKI or death in critically ill patients (Nisula et al. 2014).

Very limited evidence exists for using NGAL among the burn population, only six studies with a total of 343 adults (Howell et al. 2015; Hong et al. 2013; Sen et al 2015; Chun et al. 2017; Yang 2014; Depret et al. 2018) and one study with 22 children (Yavuz et al.

2014) have been published since 09/2019. Many of them concluded that plasma or urine NGAL are superior to SCr in AKI diagnostics in the early phase after burn injury. A study of 90 adults showed plasma and urine NGAL to be superior to SCr in predicting early AKI, but they failed to predict late-onset AKI (H. T. Yang et al. 2014). A recent study of 76 adults concluded that serum NGAL was significantly elevated in AKI patients at days 7, 14, 21 and 28 after burn injury. NGAL levels were affected by operations, septic shock and AKI. Serum NGAL was not independently associated with mortality. The study concluded that NGAL is affected not only by AKI, which must be accounted as a limitation (Chun et al. 2017). A recent study of 84 adults concluded that SCr was more accurate than NGAL in predicting AKI development in the first week after burn injury. The accuracy of SCr slightly weakened in weeks two to five, whereas the diagnostic performance of serum NGAL remained poor during the whole study period (AUC: 0.51-0.67) (Y. Kim et al. 2018). A study of 87 severely burned patients showed that elevated plasma NGAL on admission increased risk for death, dialysis or unrecovered kidney function for at least 90 days (Dépret et al. 2018).

NGAL was thought to be the “troponin of the kidneys” (Devarajan 2010). However, this insight has faced criticism due to incomprehensive knowledge of the NGAL as a biomolecule. Current laboratory equipment is claimed to be incapable of distinguishing the three different isoforms of NGAL, which makes it impossible to distinguish NGAL originating from the kidneys (Legrand et al. 2013, Glassford et al. 2013). Many other factors, such as systemic inflammation and potentially circulating extra-renal NGAL, may confound measurements, and they create a major problem when making clinical judgements (Mårtensson & Bellomo 2014).

2.10.3 Brain natriuretic peptide (BNP)

BNP was discovered in 1988. It is related to the natriuretic peptide family, which has an essential role regulating extracellular fluid volume. It is a neuroendocrine ligand secreted from cardiac myocytes after ventricular stretching (Ruskoaho 1992). BNP and NT-proBNP are both formed from proBNP, which is enzymatically dissociated during its secretion process. BNP has a 20 min. half-life vs. NT-proBNP’s 120 min. The clearance of NT-proBNP is processed via kidneys, and decreased GFR tends to raise NT-proBNP levels in plasma (Martinez-Rumayor et al. 2008; H.-N. Kim & Januzzi 2011; Tagore et al. 2008). NT-proBNP levels increase with age; this effect is accounted for in the

reference values (Maisel et al. 2008). A lower BNP was observed to be associated with a higher body mass index in noncardiac patients (BMI) (T. J. Wang et al. 2004). NT-proBNP has a validated diagnostic value in congestive heart failure, a condition that causes fluid accumulation and stretching of the cardiac muscle (Maisel et al. 2002; McCullough et al. 2002). Elevated NT-proBNP levels have also been measured as an effect of right ventricular stretch in acute pulmonary embolism (Coutance et al. 2008) and in acute respiratory distress syndrome (ARDS) (Maeder et al. 2003; Yap et al. 2004). NT-proBNP and BNP have also been investigated in several noncardiac clinical settings: In general ICU patients, BNP was elevated in those who showed worsening of kidney function at the early phase of the ICU stay (de Cal et al. 2011). Two studies showed opposite results when evaluating NT-proBNP as a marker for worsening kidney function in patients who were admitted to hospital due to acute decompensated heart failure (Legrand et al. 2014; Yamashita et al. 2010). A multicenter study showed that elevated NT-proBNP levels predicted mortality during hospitalization in general ICU patients suffering from sepsis or severe shock (Varpula et al. 2007). Two minor studies on general ICU patients have shown an association between NT-proBNP and the Sequential Organ Failure Assessment (SOFA) score (Guaricci et al. 2015; Piechota et al. 2006). The SOFA score reflects the severity of organ dysfunction during an ICU stay (Vincent et al. 1996).

Minor evidence of BNP or NT-proBNP exists among the burn population: NT-proBNP was elevated not only in those burn patients who developed abdominal compartment syndrome or pulmonary oedema as a sign of excessive fluid resuscitation (Howell et al. 2015; Friese et al. 2007) but also in patients who developed sepsis after burn injury (Paratz et al. 2014). High BNP at day three after burn injury was associated with successful fluid resuscitation and improved outcome (de Leeuw et al. 2011). A Swedish study concluded that NT-proBNP correlates with the SOFA score and the size of the burn injury (Lindahl et al. 2013).

Table 3 ABSI, Baux and modified Baux score

The Abbreviated Burn Severity Index (ABSI) (Tobiasen et al. 1982)

Parameter	Finding	Points
Sex	Female	1
	Male	0
Age (years)	0-20	1
	21-40	2
	41-60	3
	61-80	4
	81-100	5
Inhalation injury	Yes	1
	No	0
Full-thickness burn	Yes	1
	No	0
Burned TBSA%	1-10	1
	11-20	2
	21-30	3
	31-40	4
	41-50	5
	51-60	6
	61-70	7
	71-80	8
	81-90	9
	91-100	10

ABSI score and prediction

ABSI	Threat to life	Probability of survival
2-3	Very low	≥ 99
4-5	Moderate	98
6-7	Moderately severe	80-90
8-9	Serious	50-70
9-11	Severe	20-40
≥ 12	Maximum	≤ 10

Baux score (S. Baux)

Baux score = Patient's age + TBSA%

The modified Baux score (Osler et al. 2010)

The modified Baux score = Patient's age + TBSA% + 17* (*When inhalation injury exists)

2.11 Prediction of prognosis in burn patients

Many scoring formulas (Table 3) have been invented to judge the severity of burn patients' situations and additionally to evaluate their prognosis after trauma (Hussain et al. 2013). The Baux score was the first scoring system to predict the change of survival after injury (S. Baux). It takes into account the patient's age and burned TBSA%. When published in 1961, a score over 100 was considered to be a predictor of certain death and LD_{50} yield around 75. The treatment of burn patients has experienced major improvements since then, and the predictive value of the Baux score is doubted now. Osler et al. presented a modified Baux-score in 2010. They showed a 0.956 AUC for the modified Baux score in predicting death during a hospital stay with 39888 patients treated from 2000-2007 (Osler et al. 2010). Several studies of burn patients treated between 1987 and 2013 showed the modified Baux score to have 0.84-0.96 AUC in predicting death during a hospital stay (Table 4). Modern studies of LD_{50} for Baux score have set it at around 100 and LD_{100} at around 130 for patients treated in 1977-1996 (Bang & Ghoneim 1996; Wibbenmeyer et al. 2001). The latest studies performed from 2000-2008 showed improvements in survival: LD_{50} reached 110 and LD_{100} 160 with 5280 burn patients (Roberts et al.

2012). The AUC for the Baux score in predicting death was evaluated to be 0.90-0.93 in burn patients treated in 1977-1996 and 2003-2009 (Table 4). A recent Swedish study resulted in an AUC as high as 0.97 for the Baux score in predicting death in the Swedish population between 1993 and 2012 (Steinvall et al. 2016) (Table 4). The Baux score has been notably higher in nonsurvivors (Rao et al. 2006), which correlates with hospital stays after injury (Gravante et al. 2007).

The ABSI score was published in 1982 based on a study population of 590 patients from two burn centers (Tobiasen et al. 1982). It includes age, sex, TBSA%, presence of co-morbidities, inhalation injury and full-thickness burn as criteria (Table 3). Several studies have shown that an elevated ABSI score increases the risk of death in burn patients (Büttemeyer et al. 2004; Rao et al. 2006; Germann et al. 1997; Forster et al. 2011; Lumenta et al. 2008; Lionelli et al. 2005; Wibbenmeyer et al. 2001) and ABSI-score correlates with the length of a hospital stay (Gravante et al. 2007). A retrospective analysis of 2813 patients treated between 1968 and 2008 confirmed ABSI to be a fair predictor of outcome among the burn population (Forster et al. 2011). The AUC of ABSI in predicting death during a hospital stay has varied between 0.82 and 0.91 in patients treated between 1977 and 2015 (Table 4).

Table 4 ABSI, Baux and modified Baux score in predicting death after burn injury

	Years	Number of patients	AUC-ABSI	AUC-Baux	AUC-Mod. Baux	Inclusion criteria	Average or median (m) TBSA%	Average or median (m) age
Wibbenbeyer et al. 2001	1977-1996	308	0.82	0.93		Age > 60 years	13 (m)	71.5
Osler et al. 2010	2000-2007	39888			0.96	Register study	9.7	30.6
Tahir et al. 2009	2007-2008	80	0.97			TBSA > 20%	42	31
Dokter et al. 2014	1987-2009	4389			0.96	All patients admitted	6 (m)	27 (m)
Tsurumi et al. 2015	2003-2009	333	0.86	0.90	0.91	Age > 16, TBSA > 20%		
Tsurumi et al. 2015	2003-2009	189	0.83	0.81	0.85	Age < 16, TBSA > 20%		
Hussain et al. 2013	2006-2010	927	0.97	0.89		Register study		
Yoon et al. 2017	2007-2010	84	0.76			RRT patients, TBSA > 20 %	59.5	52
Brusselaers et al. 2013	2009-2011	261	0.84-0.86		0.84	All patients admitted	25.8	16.6
Steinvall et al. 2016	1993-2012	1613	0.96	0.97	0.98	All patients admitted	12.4	33.7
Queiroz et al. 2016	2010-2012	293	0.89			Age > 18	22 (m)	38 (m)
Pantet et al. 2016	1996-2013	492	0.91		0.92	All patients admitted	20 (m)	42 (m)
Heng et al. 2015	2004-2013				0.92	Age > 18, TBSA > 15%	36.5 (m)	45.7 (m)
Smith et al. 2016	2013-2015	748	0.90		0.89	All patients admitted	9.7	17.1
Salehi et al. 2017	2015-2016	238	0.86		0.84	Age > 18 years	58.3	38.3

3. AIMS OF THIS STUDY

This study's purpose was to investigate the usefulness of novel biomarkers in AKI diagnostics and their behaviour during fluid resuscitation after severe burn injury. An additional goal was to investigate factors associated with the prognosis and development of AKI and which factors predict death, AKI and long-term complications after receiving RRT for a severe burn. We also wanted to establish if a linkage exists between severe AKI and CKD and if they associate on the patients' long-term mortality.

The specific aims of this thesis were to investigate:

1. If plasma NGAL is a more rapid and accurate biomarker in AKI diagnostics than SCr or CysC during the first week after a severe burn injury (I)
2. If plasma NT-proBNP is useful in AKI diagnostics within the first week after a burn injury and does it reflect the amount of fluids given in resuscitation after injury (II)
3. What are the risk factors for AKI and death after a severe burn injury (III)
4. If Baux, modified Baux or ABSI score are accurate in predicting death after severe burn injury (III)
5. If the prognosis of early AKI differs from that of the late AKI (III)
6. If burn patients stay dialysis dependent after severe AKI (IV)
7. If CKD is a common sequela after severe AKI and has it enhanced long-term effect on mortality (IV)

4. MATERIALS AND METHODS

This thesis consists of four human studies. Studies I-II are prospective cohort studies, and studies III-IV are retrospective cohort studies.

4.1 NGAL (I) and NT-proBNP study (II)

The prospective studies were carried out between March 2013 and September 2014 in the Helsinki Burn Centre. The inclusion criteria were TBSA% above 20 or above 15 for patients aged over 60 years. All enrolled patients gave their informed consent for participation in these studies. When the patient was unable to give consent, it was obtained from the relatives. The following parameters were collected from all patients: Age, sex, BMI, TBSA%, burn mechanism, need for intubation or ventilation, escharotomies, ABSI (Tobiasen et al. 1982) and SOFA scores (Vincent et al. 1996), co-morbidities, need for RRT, duration of ICU stay and outcome. Table 5 shows the laboratory parameters measured.

Table 5 Laboratory measurements of studies I and II

NGAL study (I)

Plasma NGAL, SCr and CysC
- Arrival, 12, 24,36,48h. Thereafter daily until day 7.

NT-proBNP study (II)

Plasma NT-proBNP
- Arrival, 12, 24,36,48h. Thereafter daily until day 7.

C-reactive protein (CRP)
- Daily

Admission values
- Body temperature, arterial pH and base excess (BE)

Highest values (only first 48 h)
- Plasma sodium, potassium, glucose

Lowest values (only first 48 h)
- Plasma sodium, glucose, MAP, body temperature, arterial pH and BE

All laboratory parameters were analysed via Helsinki University Central Hospital (HUCH) laboratory services (HUSLAB) except plasma NGAL (I) and NT-proBNP (II), which were analysed by Triage®, a point-of-care device (POC) (Alere Inc., Waltham, MA, USA) that determines the levels of both biomarkers from the same test kit (Alere Triage® CardioRenal Panel) by an enzyme-linked immunosorbent assay (ELISA). It detects NGAL in the range of 15 to 1300 ng/ml and NT-proBNP in the range of 5 to 5000 pg/ml. Quality control procedures were performed according to the guidance of the manufacturer.

4.2 AKI study (III)

All ICU patients treated in Helsinki Burn Centre between January 2006 and December 2015 were collected. Excluded patients had TBSA% less

than 20 who had succumbed within 48 hours from admission and were admitted to burn centre more than 36 hours after injury. The following parameters were collected for the enrolled patients: Age, sex, burn mechanism, TBSA%, length of ICU stay, pre-existing co-morbidities (chronic cardiac-, pulmonary, hepatic, renal or neurological illness, excl. arterial hypertension), sepsis (mentioned in medical records), inhalation injury, patient intubated on arrival, need of escharotomies or fasciotomies, ABSI score (Tobiasen et al. 1982), Baux score (S. Baux), modified Baux score (Osler et al. 2010), AKI, rhabdomyolysis and need for RRT.

4.3 RRT study (IV)

All burn patients who received RRT in Helsinki Burn Centre between November 1988 and December 2015 were enrolled. All patients discharged from the burn unit were followed up until 31st December 2016. The following parameters were collected: Age, sex, burn mechanism, TBSA%, hospital stay time, pre-existing co-morbidities, sepsis , rhabdomyolysis, inhalation injury, Baux score (S. Baux) and ABSI score (Tobiasen et al. 1982). RRT records after discharge were collected from the Finnish Registry for Kidney Diseases (FRKD), a registry maintained by the Finnish Kidney and Liver Association (Finnish Registry for Kidney Diseases). This registry covers up to 98 percent of patients receiving RRT for over three months in Finland. The patients' causes of death (COD) were collected from The Causes of Death Registry maintained by The Statistics Finland (The Causes of Death Registry – Statistics Finland). The patients' COD or need for long-term RRT were recorded at 31st December 2016. COD was classified via the International Classification of Diseases (ICD-10) system by the World Health Organization (WHO). Some patients' COD were classified via the former ICD-9 system; these diagnoses were transformed into corresponding ICD-10 codes.

4.4 Statistical analyses in studies I-IV

Study I-II

Student's t-test was used for continuous variables in the NGAL study (I) and the Mann Whitney-U test in the BNP study (II) Chi-square or Fischer's Exact Test was used for dichotomous variables in both studies (I-II). Friedman analysis of variance (ANOVA) was used for repeated values, and the Wilcoxon Matched Pairs test was used post hoc (II). A multivariable regression analysis was performed for several variables to investigate which of them affect NT-proBNP values (II). The AUC of three biomarkers in predicting AKI was

determined by the receiver operating characteristic (ROC) method (I).

Study III

Student's t-test was applied for continuous variables and chi-square or Fischer's Exact Test for dichotomous variables. A multivariable regression analysis was applied for several variables to determine their impact on AKI development or death during an ICU stay. The adjusted model for Baux score in predicting death included sex, inhalation injury and pre-existing co-morbidities. AUC for Baux, modified Baux and ABSI in predicting death were determined by the ROC method.

Study IV

Student's t-test was used for continuous variables and chi-square or Fischer's exact test for dichotomous variables. A Kaplan-Meier estimator was created to estimate cumulative survival after discharge from the burn unit.

Studies I-V results were analyzed by IBM SPSS Statistics for Macintosh, Version 22.0 (Armonk, NY, USA, IBM Corp.) (I, III-IV) and by STATA, Version 12.0 (Stata Corp. LP College Station, TX, USA) (II-III). In all studies a p-value less than 0.05 was considered as a statistically significant difference.

4.5 The standard burn care (I-IV)

Patients in all four studies received standard burn care regardless of the study protocol: Resuscitation mainly by RL by the Parkland formula (4ml/kg x TBSA%), no colloids during the first eight hours. Vasopressors were used if fluid resuscitation itself was insufficient to maintain adequate hemodynamics. Bronchoscopy was performed at an early stage when inhalation injury was suspected. Operations were performed at appropriate times regardless of the ongoing studies. Preventive escharotomies or fasciotomies were performed when necessary. RRT was initiated when a patient was evaluated to benefit from treatment and directional guidelines to initiate RRT were met. However, the decision to initiate RRT was evaluated on an individual basis and not by meeting certain criteria. The general guidelines to consider RRT initiation were: Hyperkalemia (plasma potassium >6.5), severe acidosis (arterial pH < 7.15), diuresis < 200 ml/12 h, fluid retention with anuria including extremity swelling, pulmonary oedema, increased intra-abdominal pressure, plasma urea > 35 mmol/l or SCr > 500 µmol/l (5.7 mg/dl).

4.6 Definitions for AKI and rhabdomyolysis in studies I-IV

Study I and II

AKI was classified if AKIN stage I criteria were met (Mehta et al. 2007).

Study III

AKI was classified if SCr rose above 120 µmol/l, but this was not considered to be AKI if it decreased below 120 µmol/l within 48 hours from the first value.

Rhabdomyolysis was classified as a plasma CK value ≥ 5000 IU (Sharp et al. 2004)

Study IV

Rhabdomyolysis was classified as a plasma CK value ≥ 5000 IU (Sharp et al. 2004)

Studies I, III-IV

Onset of AKI was classified as “early” when encountered within five days post burn and “late” after day five (Holm et al. 1999).

4.7 Ethical considerations

Studies I and II were approved by the Research Ethics Board of Helsinki University Hospital (HUH). Studies III and IV were waived by the ethics board due to the nature of the study (study material focused only on medical records). Studies I-IV received a research permit from HUH.

5. RESULTS

5.1 NGAL and NT-proBNP study (I-II)

Nineteen patients treated between Mar 2013 and Sep 2014 in Helsinki Burn Centre were enrolled. Nine patients (47.4 %) developed AKI during the study period, and two patients needed RRT (10.5%) during their hospital stay. AKI was diagnosed in five patients via SCr alone, in three via UO alone and in one patient by both criteria. Both RRT patients survived, and their kidney function recovered. Two patients (10.5%) succumbed during their ICU stay: both had AKI and simultaneous MOF. Table 6 presents the patients' demographic data. AKI patients had a significantly higher BMI, SOFA-score at admission and higher SOFA scores during the first 7 days of their ICU stay.

SCr and CysC were significantly higher at all measuring points (except SCr at arrival and at 48h and CysC at arrival and 12h) in the AKI group vs. in the non-AKI group. NGAL was significantly higher in the AKI group only at days 4 and 5 compared to the non-AKI group. Figure 5a-c shows the concentrations of these three biomarkers after burn injury. The ROC-method's diagnostic power for AKI resulted in AUC of 0.919 for SCr, 0.866 for CysC and 0.623 for NGAL in predicting AKI (Figure 4). Plasma NGAL rose on average 72 ± 29 h (95% CI) later compared to SCr and 36 ± 43 h later than CysC in patients with early AKI using cut-off-points of 100 µmol/l for SCr, 1,4 mg/l for CysC and 400 ng/ml for NGAL. Plasma NGAL levels rose a week earlier than SCr levels in one late AKI case. When using a lower cut-off-point for plasma NGAL, 150 ng/ml (as recommended by the manufacturer of Triage® meter), the time gap of SCr and NGAL narrowed to 6 ± 20h (95% CI), but SCr was still superior to NGAL in most cases. This lower cut-off-point, however, resulted in 9/10 non-AKI patients having a false diagnosis of AKI (plasma NGAL over 150 ng/ml). Optimized cut-off-points for all biomarkers were 75 µmol/l for SCr, 0.95 mg/l for CysC and 152 ng/ml for NGAL, resulting in sensitivities of 80%, 85% and 60% and specificities of 84%, 80% and 53%, respectively.

All patients received at least 90% of the suggested resuscitation volume determined by the Parkland formula during the first 24 hours. The AKI group had significantly lower minimum BE and arterial pH during the first 48 hours. Table 7 presents the patients' resuscitation data of patients. NT-proBNP levels increased in all patients during the seven-day study period (Figure 6); a wide variation was observable among single patients (Figure 7) and even greater variation was observed in the AKI group (Figure 8). A linear association emerged between NT-proBNP and cumulative infusions given on a group level, but the association was nonsignificant in

the AKI group. A logistic regression model (Table 8) was performed with several parameters and NT-proBNP by explorative fashion, which showed a significant association with age, BMI and arterial pH at admission with NT-proBNP values.

Table 6 Characteristics and baseline parameters of patients at studies I and II.

Variable	Non-AKI (n=10)	AKI (n=9)	p
Age	48.2 ± 18.8	59.7 ± 12.4	0.14
Male sex	5 (50%)	6 (67%)	0.46
BMI	24.3 ± 2.9	35.7 ± 10.4	**0.011***
Number of co-morbidities	1.1 ± 0.88	1.9 ± 1.76	0.25
%TBSA	37.6 ± 21.4	45.6 ± 12.5	0.34
Burn mechanism (Flame:Steam)	10:0	8:1	0.28
Inhalation injury	4 (40%)	2 (22%)	0.7
Intubated on arrival	4 (40%)	5 (56%)	0.5
Need for ventilation	5 (50%)	5 (56%)	0.81
ABSI scoring	8.5 ± 2.4	10.6 ± 2.0	0.059
SOFA scoring on arrival	4.2 ± 2.9	7.8 ± 2.3	**0.015***
Highest SOFA score	7.1 ± 3.0	10.8 ± 2.6	**0.018***
Escharotomies needed	6 (60 %)	6 (67%)	0.76
Duration of ICU time	21.6 ± 10.4	34.9 ± 21	0.107
Need of RRT	0 (0%)	2 (22%)	0.12
Non-survivors	0 (0%)	2 (22%)	0.12
Grading of AKI			
AKIN 1		2 (22.2%)	
AKIN 2		3 (33.3%)	
AKIN 3		4 (44.4%)	
Type of AKI			
Early AKI		8 (88.9%)	
Late AKI		1 (11.1%)	

ABSI, Abbreviated Burn Severity Index; AKI, acute kidney injury; AKIN, acute kidney injury network; BMI, body mass index; ICU, intensive care unit; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; TBSA, total body surface area. Data are reported as mean ± SD or percentage, when appropriate.
Statistically significant difference *(P< 0.05)

Table 7 Resuscitation & laboratory data

	All	Non-AKI	AKI	P value
Patients, n	19	10 (53)	9 (47)	
Parkland, mL	13824 (8400-17280)	8680 (6600-11700)	15360 (14208-17280)	0.01
Infusions day 1, mL	21587 (16406-32031)	18300 (15436-23054)	32031 (18957-35741)	0.04
Parkland, ratio*	1.61 (1.23-2.10)	2.04 (1.23-2.34)	1.56 (1.23-1.97)	0.30
Urine output day 1, mL	1751 (810-2745)	1951 (1140-2760)	1338 (405-2525)	0.27
MAP on arrival, mmHg	89 (78-100)	93 (78-103)	86 (79-93)	0.40
Lowest MAP, mmHg	58 (52-63)	58 (57-63)	57 (49-59)	0.24
CRP on arrival, mg/L	4 (3-9)	4 (3-63)	6 (3-8)	0.90
Highest CRP, mg/L	239 (198-277)	267 (198-277)	235 (210-264)	0.55
BE on arrival, mmol/L	-5 (-10 to -3)	-6 (-9 to -3)	-5 (-15 to -4)	0.50
Worst BE, mmol/L	-10 (-13 to -5)	-7 (-10 to -4)	-13 (-18 to -11)	0.008
Arterial pH, on arrival	7.3 (7.2-7.3)	7.3 (7.2-7.3)	7.3 (7.2-7.4)	0.97
Arterial pH, lowest	7.2 (7.1-7.2)	7.2 (7.2-7.2)	7.1 (7.0-7.2)	0.002

Data are presented as median (25th and 75th quartiles), or n (%). *The ratio between calculated Parkland (4 ml) and given infusions on day 1. P-value is calculated between AKI and non-AKI patients. BE, Base excess; CRP, C-reactive protein; MAP, Mean arterial pressure.

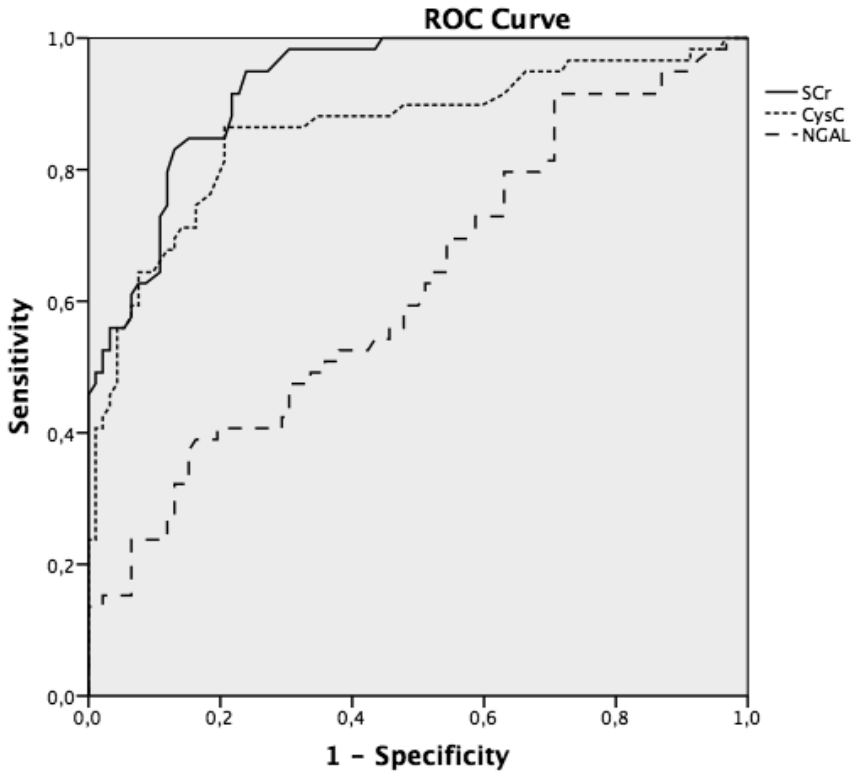


Figure 4 ROC-curves for three biomarkers in predicting AKI during first week at ICU.

Figure 5a Changes in SCr during first week at the ICU. Timepoint indicates mean value and 95% CI.

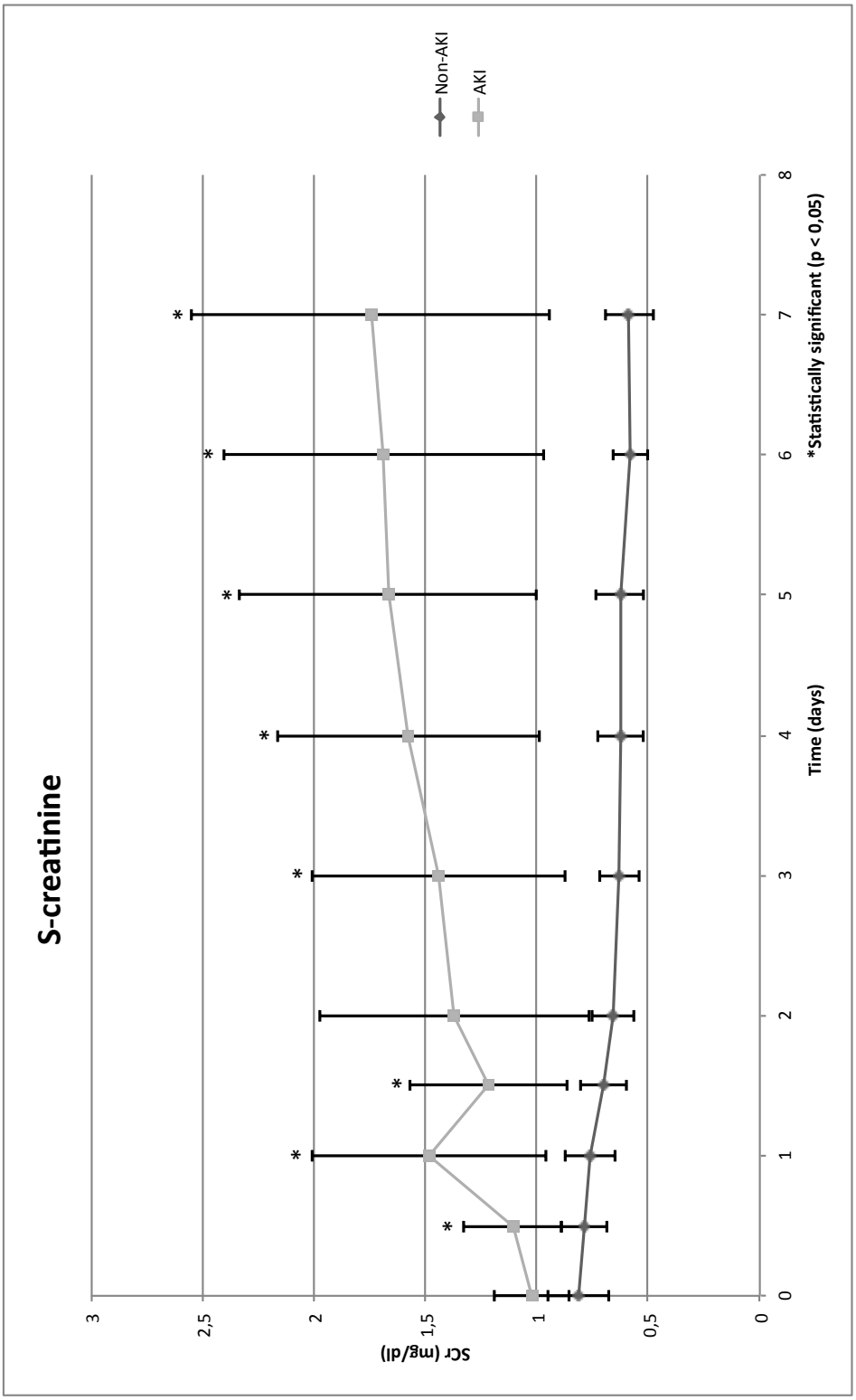


Figure 5b Changes in CysC during first week at the ICU. Timepoint indicates mean value and 95% CI.

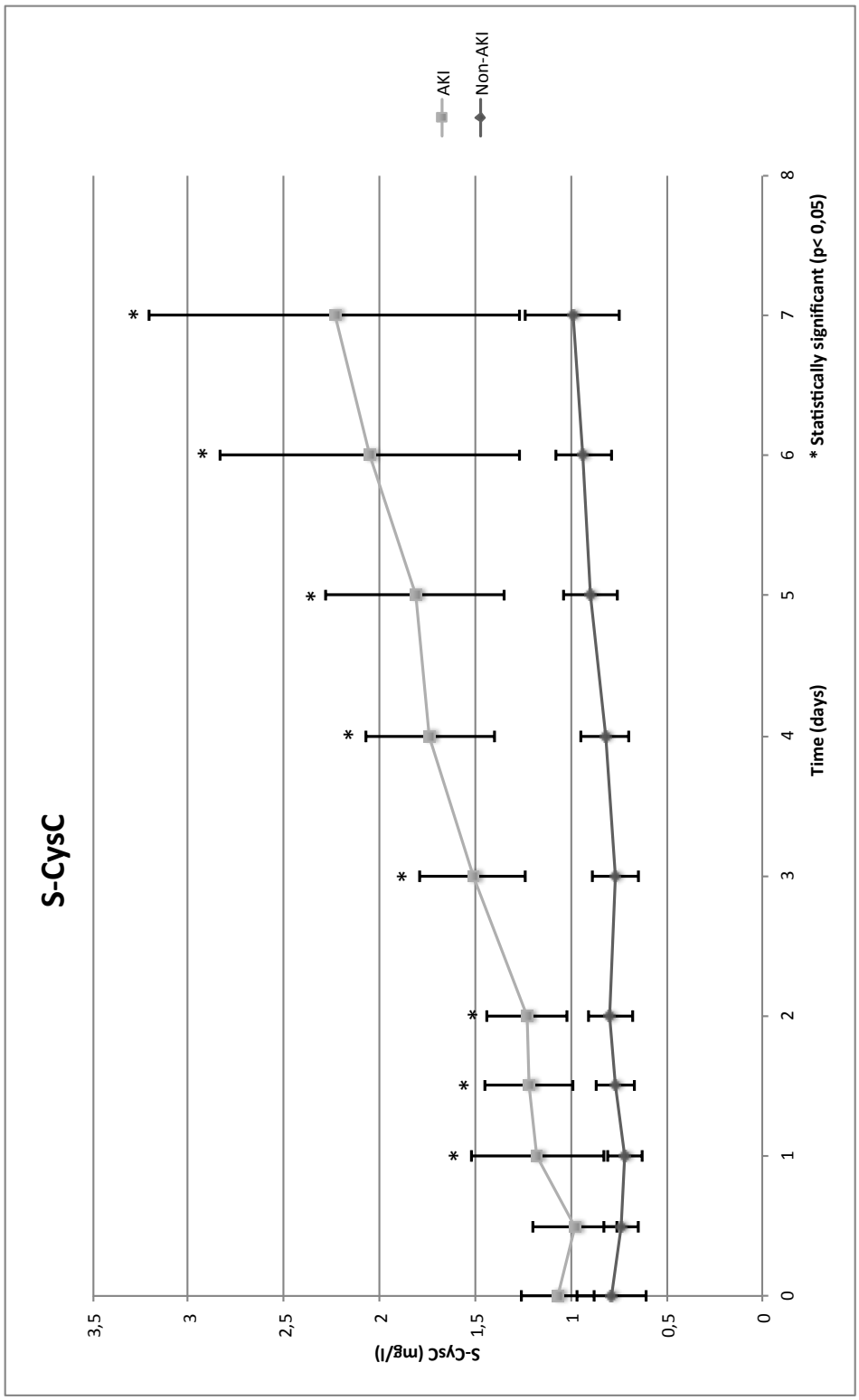
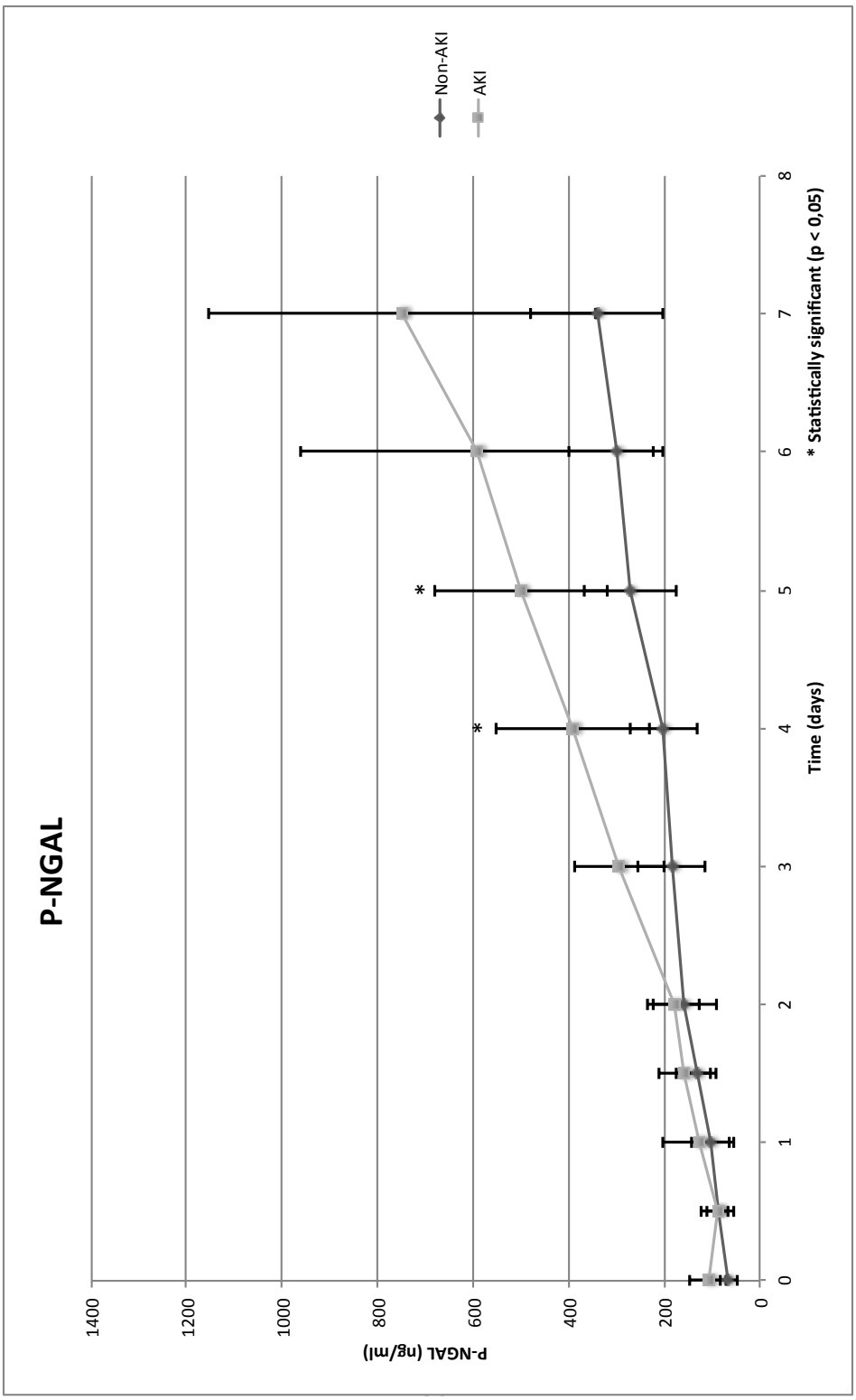


Figure 5c Changes in NGAL during first week at the ICU. Timepoint indicates mean value and 95% CI.



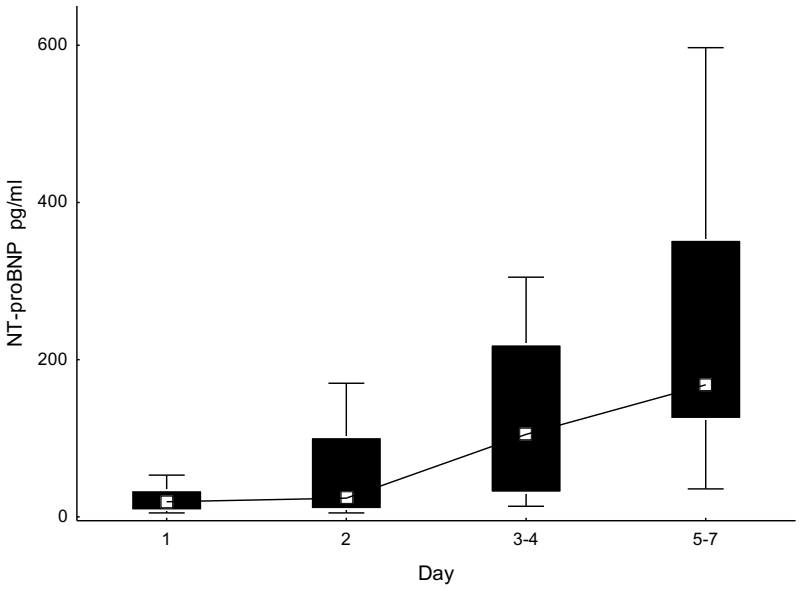


Figure 6 The increase of plasma NT-proBNP over time during the first week after admission was significant (ANOVA Chi Square = 40.69, *P <0.001*), post hoc analysis showed p values <0.001 between all time periods except between day 1 and 2 (p= 0.01) and between days 3-4 and 5-7 (p= 0.049) (not adjusted for repeated measures). Median, box = 25th to 75th quartiles, whisker = non-outlier range.

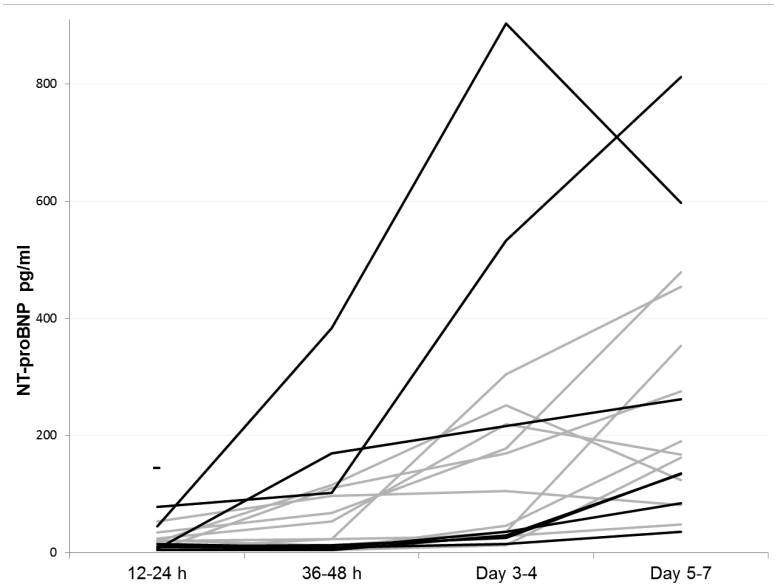


Figure 7 Plasma concentration of NT-proBNP maximum value of each patient at different intervals after injury: 12-24 hours, 36-48 hours, day 3-4, and day 5-7. Black lines = patients with AKI, grey lines = non-AKI.

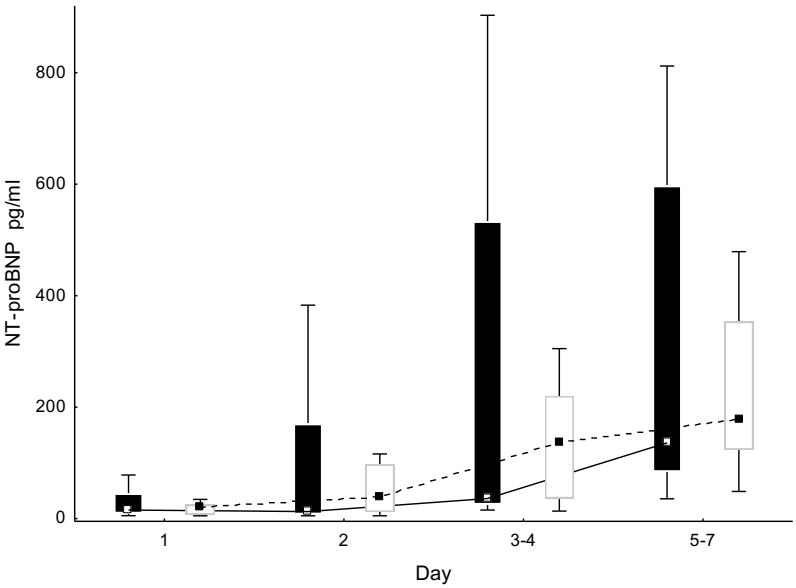


Figure 8 Plasma concentration of NT-proBNP over time by the groups of patients who developed AKI (black bars) and not (white bars). Median, box = 25th to 75th quartiles, whisker = non-outlier range.

Table 8 Multivariable regression for plasma concentration of NT-proBNP during the first week after burn

	Coefficient	SE	p value	95% CI		
TBSA%	3.4	2.0	0.09	-0.5	to	7.2
BMI	-14.4	3.9	<0.001	-22.0	to	-6.8
Age, years	3.6	1.8	0.04	0.1	to	7.0
Sex, male	-30.3	52.1	0.56	-132.5	to	71.8
pH at admission	-659.3	340.9	0.05	-1327.5	to	9.0
SOFA, highest	12.7	10.4	0.23	-7.8	to	33.1
CRP, highest	0.4	0.3	0.15	-0.2	to	1.1
Cumulative infusions	0.003	0.001	0.01	0.0	to	0.0
AKI	72.2	78.4	0.36	-81.5	to	225.8
Constant	4692.7	2494.0	0.06	-195.5	to	9580.9

Multivariable regression for panel data. Model (between) R^2 0.68, *P<0.001*, patients n=17, recordings n=63. AKI, acute kidney injury; BMI, body mass index; CRP, C-reactive protein; SOFA, Sequential Organ Failure Assessment; TBSA, total body surface area.

5.2 AKI study (III)

Between January 2006 and December 2015, 1703 patients received treatment in the Helsinki Burn Centre. 187 patients were included to study III (Figure 9). 27.3% had AKI and 11.2% received RRT during ICU stay. Demographic data of all patients included are presented in Table 9. Based on patients' medical records, none of AKI patients showed evidence of pre-existing impaired kidney function. AKI patients had significantly higher age, TBSA%, ABSI and Baux score, longer ICU stay and mortality of 52.9% vs. 7.4% in no AKI patients. Flame burn also seemed to be more common in AKI vs. no AKI patients. 41.2% of AKI patients received RRT during their hospital stay. Table 9 shows demographic parameters between AKI and no AKI patients. Two thirds of AKI patients had early AKI. Late AKI group had significantly higher burned TBSA% (57 vs 44) and higher ABSI scores (10.6 vs 9.5). All AKIs induced by hot air sauna and the vast majority of rhabdomyolysis induced AKIs (88%) occurred as 'early'. 75% of AKIs caused by hot air sauna needed RRT, all of them survived. Table 10 shows that increasing age and TBSA%, sepsis and rhabdomyolysis were independent risk factors for AKI in a multivariable regression model.

90.5% of RRT patients were men and 85.7% of RRT group had early-onset AKI. 38.1% of RRT patients received CRRT, 42.1% intermittent hemodialysis (IHD) and 19% CRRT following IHD. AKI patients receiving RRT had significantly more rhabdomyolysis (33.3%) compared to AKI patients not receiving RRT (3.3%). Age, TBSA%, ABSI, Baux score or mortality did not differ significantly between RRT patients and AKI patients not receiving RRT. In 37% of AKI patients not receiving RRT, a decision to withhold RRT in all circumstances existed, of these 64% succumbed. In 78% of nonsurvivors in AKI patients not receiving RRT had a decision to withhold RRT in all circumstances or their condition was too poor to initiate RRT.

19.8% of all ICU patients (n=187) succumbed during their hospital stay. Table 11 presents the parameters of survivors and nonsurvivors. A significant difference between survivors and nonsurvivors in the AKI group did not emerge in ABSI or Baux score. Among RRT patients, nonsurvivors had a significantly higher Baux score (108 vs 91). Increasing age, TBSA% and AKI were independent risk factors in predicting death during their hospital stay. Coefficients for age and TBSA% decreased slightly when multivariable regression analysis also included AKI. Table 10 presents odds ratios (OR). ROC curves showed 0.84 (0.78-0.91, 95% CI) for Baux score, 0.83 (0.76-0.90) for modified Baux score and 0.83 (0.76-0.90) for ABSI score in predicting death during a hospital stay (Figure

12). LD_{50} for Baux score was 112 (Figure 11).

In all patients the likelihood of AKI formed a S-shaped curve as plotted with Baux score. The likelihood of death rose rapidly after Baux score 80, especially in flame burns. The likelihood of AKI and death at Baux score 100 was ~40% and ~30%, respectively. At Baux score 70, the probability of death was ~30% in AKI patients, whereas only ~5% in all ICU patients. A linear association between Baux score and death emerged in AKI patients. The results stayed the same when all Baux curves (Figure 11) were adjusted with all variables presented in Table 10.

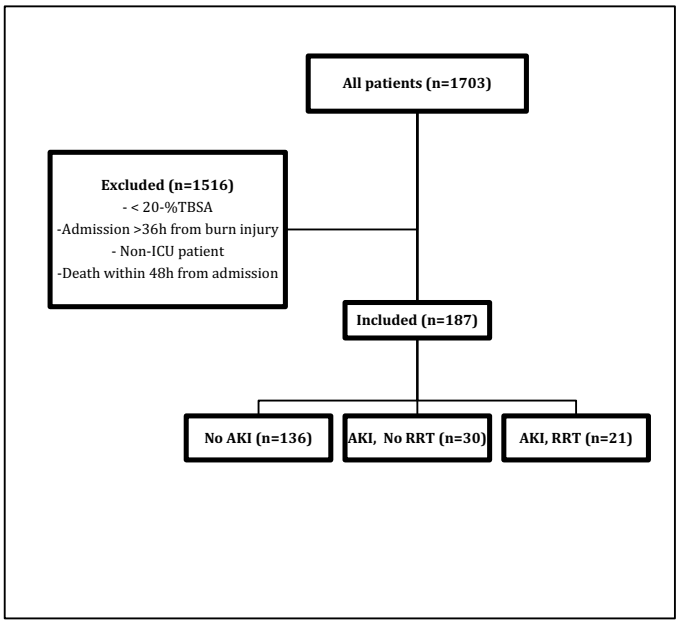


Figure 9 Overview of patients. AKI, acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy; TBSA, total body surface area.

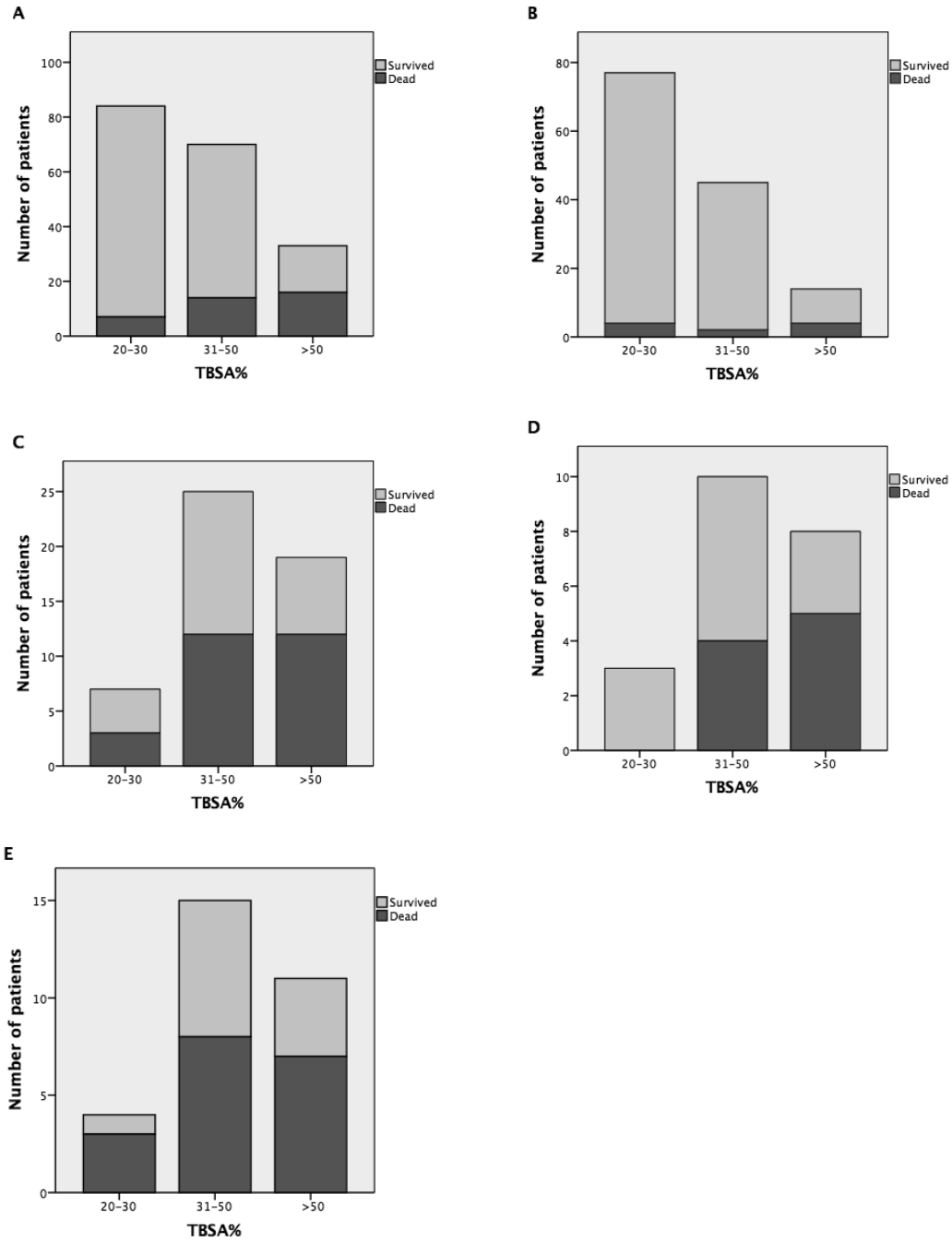


Figure 10 Distribution of survivors and non-survivors in A) all patients B) no AKI patients C) AKI patients D) RRT patients E) AKI, no RRT patients. TBSA; Total body surface area

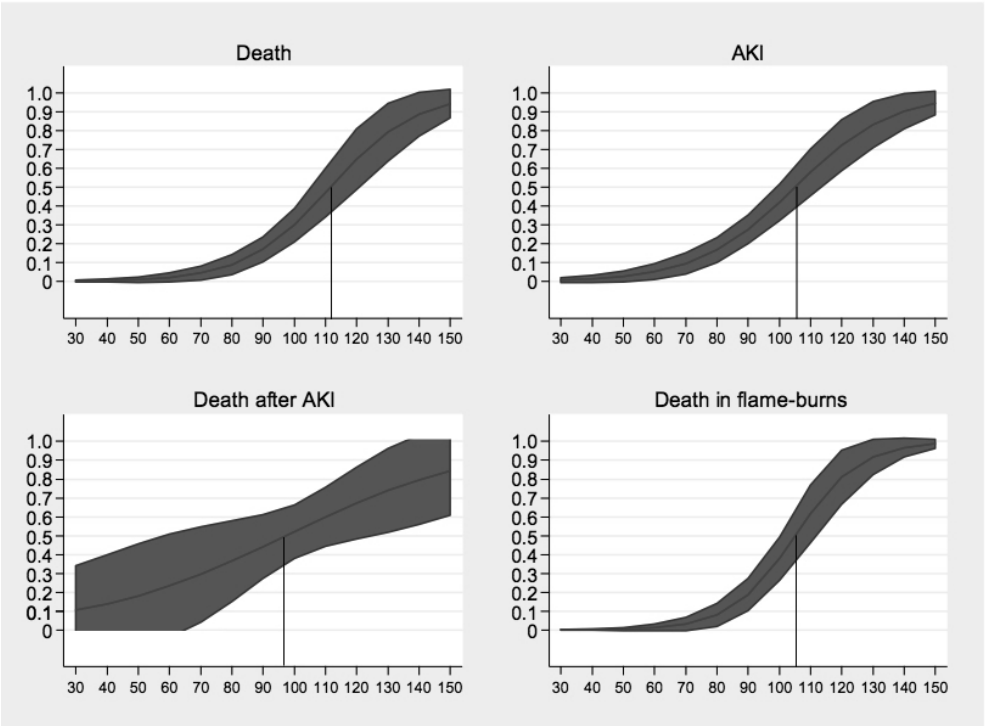


Figure 11 Baux score in x-axis and probability in y-axis. Death and AKI in all ICU patients (upper row); probability of death in AKI patients and –in patients with flame burn (lower row). Baux score predicting 50% chance for each endpoint (AKI, death) is marked with vertical line. Marked area around the curve shows 95 % confidence intervals. AKI, acute kidney injury; ICU, intensive care unit.

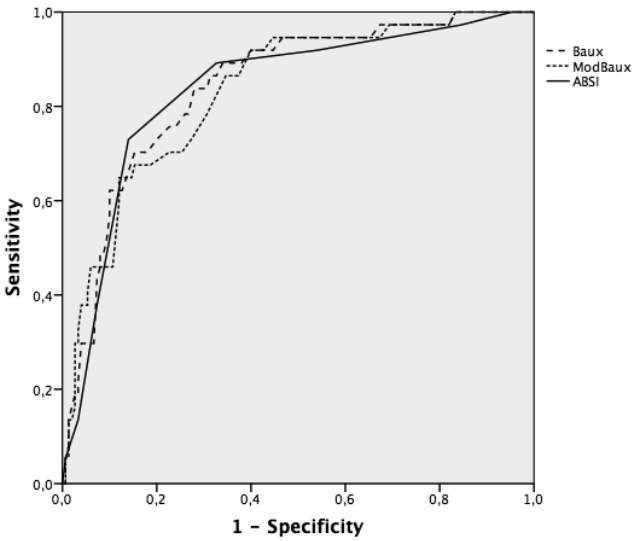


Figure 12 ROC-curves for ABSI-, Baux- and modified Baux scores predicting death during a hospital stay. ABSI, Abbreviated Burn Severity Index.

Table 9 Demographic data of study groups

Variable	All patients (n=187)	No AKI (n=136)	AKI (n=51)	AKI, No RRT (n=30)	AKI, RRT (n=21)	P1	P2	P3	P4
Age	46.4 ± 19.1 (1-87)	44.0 ± 18.9 (1-84)	52.9 ± 18.2 (17-87)	56.3 ± 18.9 (18-87)	48.1 ± 16.5 (17-76)	**0.004***	**0.002***	0.35	0.11
Burned TBSA	37.3 ± 15.7 (20-86)	33.2 ± 13.1 (20-86)	48.1 ± 17.2 (20-84)	46.6 ± 16.0 (21-80)	50.3 ± 18.9 (20-84)	**<0.0001***	**<0.0001***	**0.001***	0.46
Burn mechanism									
Flame	140 (74.9 %)	97 (71.3 %)	43 (84.3 %)	27 (90.0 %)	16 (76.2 %)	0.07	**0.04***	0.64	0.25
Sauna (hot air)	12 (6.4 %)	8 (5.9 %)	4 (7.8 %)	1 (3.3 %)	3 (14.3 %)				
Electrical	11 (5.9 %)	10 (7.4 %)	1 (2.0 %)	1 (3.3 %)	0 (0 %)				
Liquid	13 (7.0 %)	11 (8.1 %)	2 (3.9 %)	1 (3.3 %)	1 (4.8 %)				
Explosion	8 (4.3 %)	7 (5.1 %)	1 (2.0 %)	0 (0 %)	1 (4.8 %)				
Steam	3 (1.6%)	3 (2.2%)	0 (0 %)	0 (0%)	0 (0%)				
ICU stay time (days)	25.4 ± 17.4 (2-95)	23.1 ± 14.6 (2-95)	31.4 ± 22.2 (3-90)	29.0 ± 21.6 (3-85)	34.9 ± 23.3 (3-90)	**0.01***	0.16	**0.04***	0.36
ABSI-score	8.3 ± 1.8 (4-13)	7.8 ± 1.5 (4-12)	9.9 ± 1.6 (7-15)	10.1 ± 1.4 (6-13)	9.5 ± 1.8 (6-13)	**<0.0001***	**<0.0001***	**<0.0001***	0.21
Baux score	83.7 ± 22.2 (32-141)	77.2 ± 20.2 (32-133)	101.1 ± 17.9 (59-141)	103.0 ± 17.7 (59-141)	98.4 ± 18.4 (64-138)	**<0.0001***	**<0.0001***	**<0.0001***	0.37
Male sex	139 (74.3 %)	102 (75.0 %)	37 (72.5 %)	18 (60.0 %)	19 (90.5 %)	0.74	0.10	0.16	**0.02***
Inhalation injury	32 (17.1 %)	18 (13.2 %)	14 (27.5 %)	8 (26.7 %)	6 (28.6 %)	**0.02***	0.09	0.10	0.88
Intubated on arrival	91 (48.7 %)	53 (39.0 %)	38 (74.5 %)	20 (66.7 %)	18 (85.7 %)	**<0.0001***	**0.006**	**<0.0001***	0.13
Escharotomies/fasciotomies	108 (57.8 %)	63 (46.3 %)	45 (88.2 %)	26 (86.7 %)	19 (90.5 %)	**<0.0001***	**<0.0001***	**<0.0001***	1.00
Pre-existing co-morbidity	69 (36.9 %)	47 (34.6 %)	22 (43.1 %)	15 (50.0 %)	7 (33.3 %)	0.28	0.11	0.91	0.24
Sepsis	18 (9.6 %)	6 (4.4 %)	12 (23.5 %)	6 (20.0 %)	6 (28.6 %)	**<0.0001***	**0.009***	**0.002***	0.52
Rhabdomyolysis	21 (11.2 %)	13 (9.6 %)	8 (15.7 %)	1 (3.3 %)	7 (33.3 %)	0.24	0.47	**0.007***	**0.006***
RRT	21 (11.2 %)		21 (41.2 %)						
Non-survivors	37 (19.8 %)	10 (7.4 %)	27 (52.9 %)	18 (60.0 %)	9 (42.9 %)	**<0.0001***	**<0.0001***	**<0.0001***	0.23

1) AKI, no RRT vs. no AKI 2) AKI, RRT vs. no AKI 3) AKI, RRT vs. AKI, no RR. Data are reported as mean ± SD, (interval) or percentage, when appropriate. ABSI, Abbreviated Burn Severity Index; ICU, intensive care unit; TBSA, total body surface area. ***) Statistically significant difference, *P <0.05*.**

Table 10 Risk factors of AKI and death from multivariate models

Variable	OR (95%CI) for AKI	OR (95%CI) for death	OR (95%CI) for death with AKI	OR (95%CI) for death in AKI patients
Age (per 1y increase)	1.06 (1.03-1.09)	1.07 (1.03-1.10)	1.05 (1.02-1.09)	1.03 (0.99-1.07)
TBSA (per 1% increase)	1.07 (1.05-1.11)	1.09 (1.06-1.13)	1.07 (1.04-1.11)	1.04 (1.00-1.09)
Comorbidities	0.88 (0.37-2.09)	0.95 (0.38-2.39)	1.03 (0.39-2.74)	NA
Inhalation injury	2.46 (0.94-6.40)	1.77 (0.66-5.00)	1.33 (0.43-4.06)	NA
Sepsis	6.69 (1.71-26.26)	1.03 (0.26-4.09)	0.51 (0.12-2.19)	NA
Rhabdomyolysis	3.94 (1.10-14.06)	2.55 (0.66-9.83)	1.83 (0.43-7.72)	NA
AKI	NA	NA	5.97 (2.20-16.20)	NA

AKI, acute kidney injury; NA, not available; TBSA, total body surface area.

Table 11 Demographic data of non-survivors vs survivors

Variable	Survivors (n=150)	Non-survivors (n =37)	P
Age	44.3 ± 19.0 (1-84)	54.9 ± 17.4 (14-87)	**0.002***
Burned TBSA	34.2 ± 13.4 (20-84)	49.6 ± 18.5 (20-86)	**<0.0001***
Burn mechanism			
Flame	107 (71.3 %)	33 (89.2 %)	**0.03***
Sauna (hot air)	11 (7.3 %)	1 (2.7 %)	
Electrical	11 (7.3 %)	0 (0 %)	
Liquid	10 (6.7 %)	3 (8.1 %)	
Explosion	8 (5.3 %)	0 (0 %)	
Steam	3 (2.0 %)	0 (0 %)	
ICU stay time (days)	27.3 ± 17.3 (2-95)	17.5 ± 15.5 (3-51)	**0.002***
ABSI-score	7.9 ± 1.6 (4-13)	10.1 ± 1.5 (6-13)	**<0.0001***
Baux score	78.6 ± 20.5 (32-141)	104.6 ± 16.0 (59-138)	**<0.0001***
Male sex	113 (75.3 %)	26 (70.3 %)	0.53
Inhalation injury	22 (14.7 %)	10 (27.0 %)	0.09
Intubated on arrival	69 (46.0 %)	22 (59.5 %)	0.20
Escharotomies/fasciotomies	78 (52.0 %)	30 (81.1 %)	**0.001***
Pre-existing co-morbidity	52 (34.7 %)	17 (45.9 %)	0.20
Sepsis	12 (8.0 %)	6 (16.2 %)	0.21
Rhabdomyolysis	16 (10.7 %)	5 (13.5 %)	0.57
AKI	24 (16.0 %)	27 (73.0 %)	**<0.0001***
RRT	12 (8.0 %)	9 (24.3 %)	**0.009***

Data are reported as mean ± SD, (interval) or percentage, when appropriate. ABSI, Abbreviated Burn Severity Index; ICU, intensive care unit; RRT, renal replacement therapy; TBSA, total body surface area.
***) Statistically significant difference, *P <0.05*.**

5.3 RRT study (IV)

Between November 1988 and December 2015, 68 patients received RRT in the Helsinki Burn Centre. Thirty-six patients (52.9%) succumbed during their hospital stay. Table 12 presents all the demographic data of survivors and nonsurvivors during their hospital stay. None of the RRT patients had a pre-existing weakened kidney function on admission, according to the medical records. The need for RRT subsided in 26 patients (81.3% of survivors) before discharge, and no patient received RRT long-term (> 3 months) after a primary hospital stay. Six patients (18.8%) still required RRT at discharge; of these, only two patients needed long-term RRT (> 3 months) after burn center discharge. These two patients received RRT for 10.5 and 17 months before the need for RRT subsided. Of these two patients, the other patient developed CKD within five years and became RRT dependent. 56.3% of the discharged patients were alive at the end of follow-up. The average follow-up time was 7.4 years (range 5-7622 days) and 9.3 years (range 367-7607 days) in those who were alive at the end of follow-up. The number of follow-up years was 238. Figure 13 presents the Kaplan-Meier analysis of patients surviving after discharge. Five patients succumbed to burns during follow-up (underlying COD (ICD-10: T20-32.9); this occurred within 50 days from discharge. One patient died due to to CKD (underlying COD ICD-10: N03, N18-19), and eight patients succumbed due to other reasons. The one-year mortality after discharge was 18.8%; 83% occurred due to burns. Figure 14 presents the flow chart of patients' follow-up.

Table 12 Demographic data of patients

Variable	All patients (n=68)	Survived (n=32)	Succumbed (n=36)	P
Age	49.0 ± 13.1 (17-76)	47.4 ± 12.7 (19-76)	50.5 ± 13.4 (17-75)	NS
Burned TBSA	43.0 ± 19.2 (7-90)	37.3 ± 17.2 (7-77)	47.9 ± 19.6 (10-90)	**0.03***
Burn mechanism				
Flame	52 (76.5 %)	22 (68.8 %)	30 (83.3 %)	NS
Sauna (hot air)	6 (8.8 %)	4 (12.5 %)	2 (5.6 %)	
Electrical	3 (4.4 %)	3 (9.4 %)	0 (0 %)	
Liquid	3 (4.4 %)	1 (3.1 %)	2 (5.6 %)	
Scald	2 (2.9 %)	1 (3.1 %)	1 (2.8 %)	
Explosion	1 (1.5 %)	1 (3.1 %)	0 (0%)	
Other	1 (1.5 %)	0 (0 %)	1 (2.8 %)	
Hospital stay (days)	36.9 ± 24.8 (2-111)	54.0 ± 20.6 (15-111)	21.7 ± 17.2 (2-65)	**< 0.001***
ABSI score	8.7 ± 2.0 (5-14)	8.2 ± 1.8 (5-11)	9.2 ± 2.0 (5-14)	**0.04***
Baux score	91.5 ± 19.1 (46-138)	84.1 ± 17.8 (46-113)	97.8 ± 18.1 (50-138)	**0.003***
Male sex	58 (85.3 %)	26 (81.3 %)	32 (88.9 %)	NS
Inhalation injury	17 (25 %)	9 (28.1 %)	8 (22.2 %)	NS
Pre-existing co-morbidity	25 (36.8 %)	13 (40.6 %)	12 (33.3 %)	NS
Sepsis	25 (36.8 %)	11 (34.4 %)	14 (38.9 %)	NS
Rhabdomyolysis	22 (32.4 %)	9 (28.1 %)	13 (36.1 %)	NS
Early AKI (<5 days)	36 (52.9 %)	25 (78.1 %)	22 (61.1 %)	NS
Non-survivors	36 (52.9 %)			

Data are reported as mean ± SD, (range) or percentage, when appropriate. P-values are calculated between survived and succumbed patients. ABSI, Abbreviated Burn Severity Index; AKI, acute kidney injury; NS, not significant; RRT, renal replacement therapy; TBSA, total body surface area. ***) Statistically significant, *P <0.05***

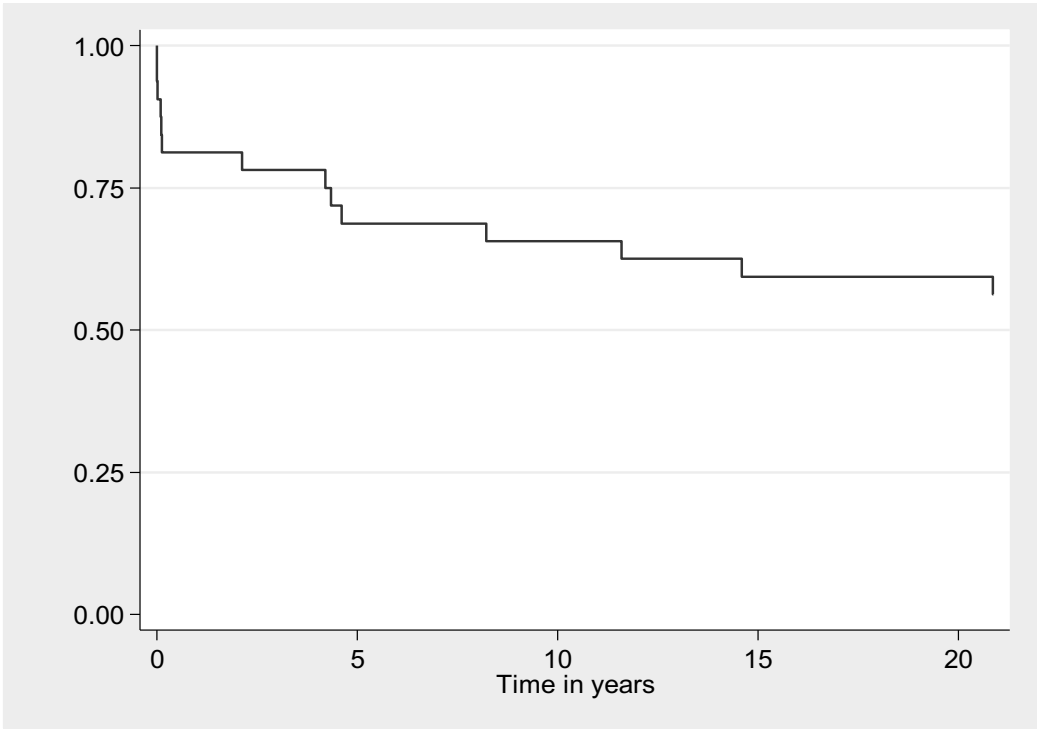


Figure 13 Kaplan-Meier analysis of patients' survival after discharge.

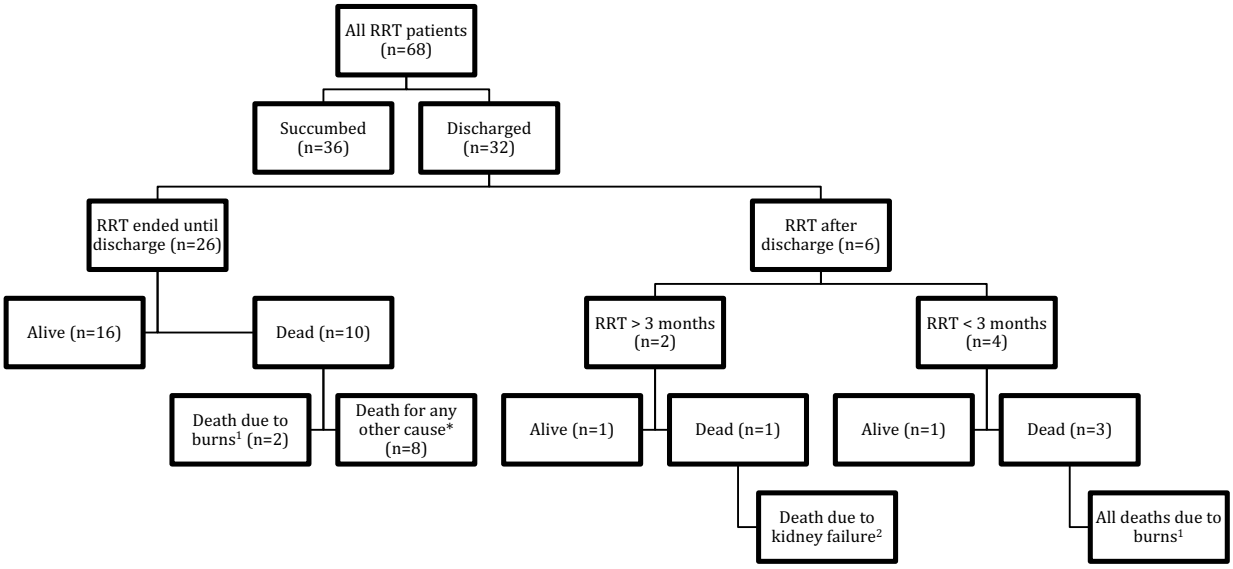


Figure 14 Flow chart of patients' survival

1) ICD-10: T20-32.9 2) ICD-10: N03, N18-19 *) COD not related to burns or kidney failure.

6 DISCUSSION

6.1 Main findings

AKI was relatively common among critically ill burn patients, and it notably increased the mortality. Plasma NGAL rose in nearly every patient during the first week after admission to the ICU. NGAL failed to rise in patients with AKI before a rise was seen in SCr, except in one patient with late AKI. Plasma NGAL rose over time by the end of the study period, and a rise was seen in nearly all patients having AKI or not. A diagnostic value of three biomarkers measured by the ROC method showed NGAL had a notably lower value than SCr or CysC (I).

Plasma NT-proBNP showed a positive correlation to cumulative infusions and older age but also a negative correlation with the body mass of the patients in a multivariable regression model. A great variation existed between single patients in absolute values of NT-proBNP. An association between AKI and NT-proBNP was not observed (II). 27.3% of burn-ICU patients developed AKI during their stay, and 19.8% died in hospital. Patients who died had a more extensive burn injury, older age, and higher ABSI and Baux score. 73% of nonsurvivors had AKI. Age and TBSA% were independent risk factors for death during an ICU stay. AKI increased the risk of death to nearly 6-fold in multivariable regression analysis. ABSI, Baux and modified Baux score at arrival nearly equally predicted death during an ICU stay. Age, TBSA%, rhabdomyolysis and sepsis were individual risk factors for AKI during ICU stay. A difference in outcome could not have been provided between early and late AKI patients (III). The need for RRT had subsided at discharge phase in 81.3% of patients who underwent RRT during ICU stay and were discharged. Of those whose need for RRT continued after discharge, 67% needed RRT for less than 6 months. COD was potentially related to the AKI encountered during acute ICU stay in one patient during follow-up. The linkage of these two aspects remained unknown (IV) due to the long follow-up time and events occurring between discharge and death.

6.2 Plasma NGAL in AKI diagnostics (I)

The results show that a constant rise in plasma NGAL on a group level could be observed during the first week at the ICU (Figure 5c).

The AKI classification in study I (AKIN, UO or SCr) is problematic due to SCr being one of the criteria for AKI that involves a major risk for circular reasoning. Although this risk exists, we expected NGAL to react faster than SCr in developing AKI. NGAL failed to diagnose AKI before SCr on an

individual level, except in one late AKI case that occurred on the 14th post-burn day. In Figure 4 plasma NGAL shows a poor AUC determined by the ROC method compared to SCr and CysC in AKI diagnostics. The number of participants was limited, so it was impossible to evaluate the diagnostic power of three biomarkers on certain timepoints with sufficient statistical power. Otherwise, more information would have been provided about their use in primary diagnostics.

Our findings were mainly opposite to those in previous papers published on the same subject, though it must be noted that these studies contain inconsistencies in their designs and participants. A study of 22 burned children showed that NGAL was significantly elevated compared to SCr at day one and day five in patients who developed AKI as defined by the RIFLE criteria. 83% of AKI patients in that study had a mild AKI (RIFLE: Risk), and only one patient was classified as “Injury.” Moreover, 91% of the patients had scald injuries. All patients had recovered kidney function within a few days after their arrival (Yavuz et al. 2014). Study I included only one patient aged < 18 years (5.3%), and nearly all patients (94.7%) in study I had flame injuries. Flame burns often deepen and extend the burn injury and also pose the risk of inhalation injury (Aldemir et al. 2005). These factors perhaps cause the tendency for NGAL levels to rise due to nonrenal causes (Chun et al. 2017).

A study of 30 burned adults showed that NGAL was significantly elevated in AKI vs. non-AKI patients 4, 12 and 24 hours after admission, whereas SCr did not differ between groups. NGAL had also a better AUC in predicting AKI 4 hours after injury as defined by RIFLE criteria (Sen et al. 2015). The determination point for AUC was 4 hours after admission, and the researchers’ definition of AKI met at least the criteria of “Injury” as defined by RIFLE (Table 1). SCr is problematic in the early phase of AKI diagnostics, because it is known to react slowly to rapidly deteriorating kidney function (Nguyen & Devarajan 2008). Despite the study having a similar study population to our study I, the results differed notably between the two studies. A potential explanation for that is that the definition of AKI differed between studies: The definition used in study I allowed diagnosing AKI with milder criteria than Sen et al did (Sen et al. 2015). One aspect is also hemodilution, which was not taken into account. A great volume of infusions decrease SCr values and interrupt measuring.

The largest study on this subject (90 patients) showed that NGAL had better AUC in predicting early AKI (onset < 5 days) development on arrival and three and six hours from injury, whereas SCr was more accurate at 12, 24 and 48 hours from injury. AKI was defined by

RIFLE criteria. Both SCr and NGAL were poor in predicting late AKI development. Results showed that the accuracy of SCr in predicting early AKI increased towards 48h after arrival, whereas the accuracy of NGAL tended to decrease (H. T. Yang et al. 2014). This possibly suggests that levels of NGAL increase over time in all burn patients, which enhances the risk for false positive results in patients not having AKI.

A small study of 15 burned adults concluded that NGAL was significantly more elevated in AKI patients 48 hours after injury compared to non-AKI patients, whereas the same thing was not observed with SCr. However, they also noted that levels of NGAL tended to increase from arrival in all burn patients, whether or not the patients had AKI (Howell et al. 2015). We observed the same effect in study I.

A study of 45 burned adults with >20% burned TBSA showed NGAL significantly elevated compared to SCr in day one, three and seven after burn injury. Plasma NGAL on day seven was the best predictor for AKI development (Hong et al. 2013). Nearly all AKIs (89%) were classified as “early” in study I, whereas in that study all AKIs were classified as “late.” Over 70% of those AKI patients died, and the most common COD was MOF accompanied by sepsis. Both of these are conditions with systemic inflammation, a potential source of extra-renal NGAL.

Previous publications have shown that NGAL is a potential biomarker after severe burn injury, and they highlight NGAL as superior to SCr in AKI diagnostics. NGAL is represented in three forms in the human body, and these forms cannot be distinguished with current POC devices (Legrand et al. 2014; Mårtensson & Bellomo 2014). This problem, which has not been brought up in previous publications, is also present in study I. A more recent paper highlights burned TBSA%, systemic inflammation and sepsis as confounding factors for rises in NGAL levels (Chun et al. 2017). The study of 76 patients noticed NGAL to be elevated also in those who did not develop AKI. Study I also observed this.

A study of 84 subjects investigated diagnostic performance of plasma NGAL compared to SCr one to five weeks after burn injury. It concluded that SCr was more accurate in predicting AKI development during the first week compared to plasma NGAL. The diagnostic performance of SCr decreased at measuring points week two to five, while performance of NGAL remained poor throughout the study. The study also showed that NGAL rose parallelly in both AKI and non-AKI patients during the first week after burn injury, with nearly equal concentrations on a group level (Y. Kim et al. 2018). Study I also observed this aspect

(Figure 5c). High NGAL on arrival predicted later development of a major kidney event in a recent cohort of 87 burn patients (Dépret et al. 2018). Patients who underwent RRT showed high NGAL levels (>980ng/ml) in study I. This potentially suggests that NGAL of renal origin represents tubular injury and has potential in AKI diagnostics if confounding extra-renal sources of NGAL can be ruled out.

Impairment of renal function was not observed even though NGAL levels constantly rose over time, and in nearly all patients the cut-off-point of 150 ng/ml was achieved. Two patients even exhibited NGAL levels of >600ng/ml. This may suggest that current laboratory diagnostic equipment cannot reliably measure renal NGAL levels in severely burned patients. It remained unknown which isoforms of NGAL were detectable with the used POC device (Alere Triage®).

We could not conclude that NGAL levels rose faster than SCr in patients who developed AKI. This validates our findings.

6.3 Plasma NT-proBNP in AKI diagnostics and its behaviour during acute fluid resuscitation (II)

Study II's population was the same as study I's, 19 consecutive patients treated in Helsinki Burn Centre between 2013-2014. A constant rise on a group level was observed after repeated measurements of NT-proBNP during the first week after burn injury. A greater variance was seen among AKI patients (Figure 8). A multivariable regression analysis revealed that changes in NT-proBNP correlated with cumulative infusions adjusted for variables presented in Table 8. We also noticed correlation with respect to older age and lower BMI. The reference values of NT-proBNP take into account the age of the patient and therefore vary in different age groups (Maisel et al. 2008). High levels of NT-proBNP have also been observed in low BMI non-cardiac patients (T. J. Wang et al. 2004). We observed the same effect in study II. This effect is thought to be related to fat tissue's ability to breakdown circulating NT-proBNP (Sarzani et al. 1996). No association was observed between AKI and higher NT-proBNP; however, this aspect remained unclear, most likely due to the small sample size.

High concentrations of NT-proBNP were detected in two patients (Figure 7). Of these, one had pre-existing atrial fibrillation, and the other needed RRT. Both are conditions in which the patient's ability to tolerate great amounts of volume intake is restricted. Accordingly, this causes stressed volume increase (Spiegel 2016) and thus possible secretion of NT-proBNP into the circulation due to increased stretch of the cardiac muscle (Ruskoaho 1992). We noticed

variations between patients in circulating levels of NT-proBNP (Figure 7), which possibly indicates that individual tolerance to volume load has an essential role in NT-proBNP secretion. In addition, capillary leakage and systemic vasodilatation caused by systemic inflammation at an early stage after burn injury results in a decrease in cardiac peptide secretion (deLeeuw et al. 2011, deLeeuw et al. 2016). Based on recent evidence and our findings, several parameters and the clinical situation affect circulating NT-proBNP values. Based on these findings, NT-proBNP might be a beneficial biomarker in guiding fluid resuscitation after burn injury. However, a larger sample size and comprehensive consideration of confounding factors are mandatory before NT-proBNP can be utilized routinely in clinical practice.

6.4 Incidence of AKI in severe burns (III)

Study III included 187 patients, retrospectively collected, treated in the Helsinki Burn Centre between 2006 and 2015.

Study III concluded the incidence of AKI to be 27.3% and an overall mortality of 19.8%. Table 2 shows the range in the incidence of AKI between earlier studies. The type of patients included and the definition of AKI are the most likely causes for this observation. Over 20 different definitions for AKI have been presented during the past decades (Brusselaers et al. 2010). This makes it impractical and even impossible to compare studies with each other unless they have similar patient cohorts and definitions of AKI.

Elevated SCr levels are common among the burn population on arrival at the ICU (Yim et al. 2015). Thus, by using an absolute value of 120 µmol/l (1.4 mg/dl) as a definition for AKI instead of a percentage-based rise, we had a higher sensitivity for the diagnosis of AKI in study III. In study III, over a third of AKI patients (37%) showed SCr > 100 µmol/l (1.1 mg/dl) on ICU arrival, which makes AKI diagnostics challenging when using percentage-based classifications, as Table 1 shows. However, using SCr in AKI diagnostics is known to be impractical in rapidly progressing AKI (Nguyen & Devarajan 2008). A recent American cohort of 1040 ICU burn patients, in which AKI was defined by AKIN (without diuresis criterion), showed that a majority of patients developed AKI (58%). This definition for AKI and their study design is one of those closest to study III. A vast majority of patients in this American study had mild AKI, which resulted in moderate mortality. These findings indicate that many patients with major burn injury have a transient SCr rise that subsides rapidly. Study III also observed this trend. The proportion of patients having AKI increased along with increase in TBSA%, likewise

shown in Figure 10.

6.5 The use of RRT to improve outcome (III)

Twenty-one patients received RRT in study III (41.2% of AKI patients) between 2006 and 2015. The number of patients receiving RRT has stayed minor over the years (~2.5 patients per year). A significantly greater proportion of RRT patients were males in study III, and rhabdomyolysis was more common compared to the rest of the AKI patients (Table 9). Study III's RRT patients had reduced mortality compared to the rest of the AKI patients; however, this difference (43% vs. 60%) did not reach statistical significance. The mortality of RRT patients has decreased from 63% to 43% (Mustonen & Vuola 2008) in comparison with the earlier study from the Helsinki Burn Centre; therefore, we could have expected the groups to have a significant difference in mortality in study III. The most likely reason for this is the limited sample size. A major confounding factor in estimating the protective effect of RRT is that 37% of AKI patients who did not receive RRT had a decision made to withhold RRT in all circumstances. Of these, 64% succumbed during their ICU stay. The decision not to initiate RRT has potentially added to the poor outcome of these patients. It is likely that most of them had such a poor prognosis of survival that they would not have benefited from RRT. Making strong conclusions about the usefulness of RRT initiation to reduce mortality is limited by this biased patient selection. As the study was not a randomized, controlled trial, study III cannot reliably evaluate the effect of RRT.

6.6 Risk factors for AKI and death during ICU stay (III)

Table 10 shows that study III concluded that increasing age, TBSA%, sepsis and rhabdomyolysis were independent risk factors for AKI development during an ICU stay. However, due to the small sample size, confidence intervals were very wide except for age and TBSA%. Therefore, study III merely reflects previous evidence when rhabdomyolysis and sepsis increased the risk for AKI development (Wu et al. 2016; Stewart et al. 2013). The ORs for age and TBSA in predicting AKI were on the same scale as shown in previous evidence among severely burned patients (Clemens et al. 2016; Queiroz et al. 2016). Study III could not verify other risk factors for AKI development, because the lack of a sufficient number of patients limited performing a more extensive multivariable regression analysis.

The proportion of inhalation injury was significantly higher in the AKI vs. no AKI group (Table 9), but multivariable regression analysis failed to demonstrate it as a risk factor for AKI

(Table 10). This is assumed to be due to the small sample size, because an earlier pooled analysis has confirmed inhalation injury as a risk factor for AKI (Wu et al. 2016).

Pre-existing medical conditions had no association with AKI development or death in study III. Two earlier studies of burn patients concluded that pre-existing medical conditions did not increase the risk of death, and co-morbidities were not more common in AKI patients compared to patients without AKI (Palmieri, Lavrentieva & Greenhalgh 2010b; Pompermaier et al. 2015). A more extensive American study concluded that pre-existing conditions increased the risk of death. However, the impact varied depending on the type of illness (Thombs et al. 2007). Study III did not take into account any coefficienting for pre-existing conditions. Table 10 shows increasing age, TBSA% and AKI as individual risk factors for death.

Flame burn was over-represented in nonsurvivors vs. survivors (Table 11). Earlier evidence has shown flame burns over-represented in nonsurvivors, likely due to the nature of flame burn injuries being more severe and having a high probability of causing inhalation injury (Aldemir et al. 2005; Mustonen & Vuola 2008).

Conflicting evidence exists about the effect of female sex with respect to the outcome after burn injury (Coca et al. 2007; McGwin et al. 2002; Queiroz et al. 2016). A larger Swedish study of 1119 individuals did not find sex having an effect on mortality (Steinvall et al. 2011). An American cohort study concluded that females aged <60 years had increased risk for death, whereas older women did not (McGwin et al. 2002). Another American study repeated these findings and concluded that females aged 30-59 years had an increased risk for death (O'Keefe et al. 2001). It must be emphasized that study III included only 48 women, which limits making strong conclusions from this study.

Figure 10 shows a notable increase in mortality in patients with co-existing AKI when evaluating the overall unadjusted effect of AKI to increase mortality. The mortality stays around ~40% (TBSA 20-30%), ~50% (TBSA 31-50%) and ~65% (TBSA >50%), whereas corresponding proportions in the same groups without co-existing AKI were ~5%, ~7% and ~30%, respectively.

6.7 Early vs. late AKI and outcome (III)

No strong evidence of reduced mortality was shown among early AKI patients (onset within five days from admission) compared to late AKI patients. A circulation deficit and a lack of oxygen to the kidneys plays a role in early AKI, whereas late AKI is usually a part of MOF with limited treatments

available (Holm et al. 1999). Early studies have concluded that early onset AKI is associated with better outcomes than late onset AKI (Aikawa et al. 1990, Davies et al. 1994), but contrary evidence has surfaced since then (Mustonen & Vuola 2008; Holm et al. 1999; Witkowski et al. 2016; Schneider et al. 2012; Mosier et al. 2010). However, these studies, have different definitions for early and late onset AKI and also for AKI itself, which makes it impossible to compare them with each other, thus limiting their usefulness in this respect. Study III's late AKI patients were significantly older and had significantly higher ABSI score than the early AKI patients. In addition, 50% of early AKI patients received RRT, compared with only 24% of late AKI patients. As mentioned earlier in the thesis, AKI patients who did not receive RRT had more pre-existing conditions, and some were withheld from receiving RRT. With respect to these findings in study III, the better outcome of early-onset AKI patients can be explained by less severe burn injuries, potentially fewer pre-existing conditions and perhaps by the better-known response of early-onset AKI to fluid resuscitation and other supportive treatments.

6.8 The prediction of prognosis by ABSI, Baux and modified Baux score (III)

Study III showed equal AUC determined by the ROC method for Baux (0.84), modified Baux (0.83) and ABSI score (0.83) in predicting death during an ICU stay (Figure 12). Table 4 shows a variation in Baux score between 0.81 and 0.97 AUC in predicting death during a hospital stay. A Swedish study concluded as high as 0.97 AUC with 1946 burn patients (Pompermaier, Steinvall, Elmasry, et al. 2017). In contrast, the modified Baux score has shown 0.84-0.98 AUC and ABSI score 0.76-0.97 AUC in predicting death (Table 4). Study III's results indicate that despite the scoring formulas being old and based on limited study populations, they are still fair predictors for outcome. Our sample size was notably smaller than in most studies presented in Table 4. This increases the possibility of coincidence affecting the prediction power. However, it can be speculated that the decline in prediction can be explained through modern advancements in critical burn care that results in better patient outcomes over time (Akerlund et al. 2007). Study III indicated the Baux score 112 as LD_{50}, which has improved from earlier decades (LD_{50} ~100) (Wibbenmeyer et al. 2001; Bang & Ghoneim 1996), and it is on the same scale with studies conducted during the same era (LD_{50} ~110) (Roberts et al. 2012; Steinvall et al. 2016). These values are remarkably higher than those in the early 1960s when the Baux score was presented (LD_{50} ~75) (S. Baux). Figure 11 shows that the relationship between Baux

score and the probability of death and the shape of the curve is comparable with earlier evidence (Tsurumi et al. 2015). The risk of death is small with a Baux score <80, but after 80 the risk of death increases, and the increase is even greater in flame burns. It must be noted that flame burn was the aetiology of burns in 75% of patients in study III. The risk of death increases more linearly in AKI patients but is notably higher compared to all patients with small Baux scores (<80). The LD_{50} was 112 in all patients; the corresponding number was 96 in AKI patients. This highlights that AKI is an individual factor for poor outcome.

6.9 The mortality after need for RRT (IV)

Nearly 53% of patients receiving RRT in study IV succumbed during their hospital stay. This proportion of mortality is notable, but it has decreased from earlier studies among burn patients who received RRT during their hospital stay (Sánchez-Sánchez et al. 2016; Holm et al. 1999; Leblanc et al. 1997). One-year mortality after discharge was 19% in study IV, which is comparable with general ICU patients having received RRT during their ICU stay (De Corte et al. 2016). However, mortality is higher than in burn patients not receiving RRT in the ICU setting (Pavoni et al. 2010).

83% of deaths during the first year were due to burns (underlying COD, ICD-10: T20-32.9), all of which occurred within 50 days from discharge. CODs of these events were similar to those who died during a hospital stay. The most common CODs were pneumonia (ICD-10: J12-18.9) and ARDS (ICD-10: J80). During the entire follow-up, over half of the deaths (8/14, 57%) were caused by nonrenal or nonburn aetiology. Over half of these deaths occurred due to cardiovascular events (ICD-10: I20-24.9, I60-64). A registry study of hospitalized patients has concluded that AKI patients had a higher risk for later development of cardiovascular disease. The risk correlated with the severity of AKI (Choi et al. 2010). Two other studies have also concluded that burn patients have an increased risk for a later myocardial infarction (Abu-Sittah et al. 2012; Thalji et al. 2017).

Overall, two registry studies found an increased all-cause mortality in burn patients after discharge compared to matched controls in the general population (Duke et al. 2015; Mason et al. 2018). Younger age and the absence of pre-existing conditions predicted good survival after burn injury, whereas higher age increased the risk of death immediately after discharge (Nitzschke et al. 2017; Pompermaier, Steinvall, Fredrikson, et al. 2017). After reviewing the patients who died shortly after discharge (within 50 days), it was noticed that they were discharged at too early a phase after their burn injury from the burn unit and that in some cases RRT was still in

progress. These actions have potentially contributed to the poor outcome. Finally, the number of patients remaining to follow-up was small, limiting the ability to make conclusions between CODs and AKI.

6.10 Long-term need for RRT after burn injury and RRT (IV)

The need for RRT continued after discharge in six patients (19% of survivors). Only in two patients (6% of survivors) did the need exceed 3 months. These patients received RRT constantly for 10.5 and 17 months before need for RRT subsided (Figure 14). Study IV showed that burn patients receiving RRT had a better kidney function recovery rate than in a study of general ICU patients receiving RRT (De Corte et al. 2016), However, in their study, those who remained dialysis dependent had an already elevated baseline SCr, whereas none of the patients in study IV had previous kidney dysfunction.

One patient developed CKD several years after initial recovery of kidney function. However, this patient required health care services not related to the burn injury after the initial hospital stay due to burns. Linkage of the CKD and AKI remained unknown. The medical records for this patient were assessed, and the documentation was deemed adequate.

Only two registry studies to our knowledge have evaluated the relationship between burn injury and long-term impairment of kidney function. A Finnish registry study concluded that the risk for ESRD increased after need for health care services due to burns compared to the general Finnish population. This study kept the linkage of burn injury and impairment of kidney function plausible, though exact explanations remained unknown. Their study failed to mention essential factors, such as the severity of burn injury, possible burn-related AKI or need for RRT relating to burn injury; thus, their conclusions cannot be extrapolated to burn related AKI. The study included partly same patients as study IV (Helanterä et al. 2016). An American registry study concluded burn-induced AKI as risk factor for ESRD and for the need of chronic dialysis one year after injury (Thalji et al. 2017). The proportion of dialysis-dependent patients one year after injury was 3.8% in study IV, whereas an American register study found it to be 4.6% (Thalji et al. 2017). In a recent American cohort of 170 burn patients 21% of patients received RRT at the discharge and 9% after six months; corresponding proportions were 19% and 6% in study IV, respectively (Chung et al. 2018).

Burn-related AKI or AKI for any other reason is potentially an accelerating factor for underlying weakened kidney

function (acute on chronic), and evidence suggests this plausible, even with completely normalized SCr after AKI in non-burn population (Chawla & P. L. Kis immel 2012; Jones et al. 2012) In conclusion, the later worsening of kidney function with this one individual patient (who died after CKD during follow-up) could have been accelerated due to burn-induced AKI, but this remained unknown.

7. LIMITATIONS

Studies I and II included only 19 patients, which limited the ability to make strong conclusions on certain aspects. We were unable to investigate biomarkers at certain time points due to too small a sample size, which would have provided further information on their diagnostic power in time to time variation. Current laboratory equipment cannot distinguish between the different isoforms of NGAL, so it is impossible to say whether the observed rise of NGAL levels in study I is from renal aetiology, suggesting tubular injury. We did not measure objective parameters describing cardiovascular status by invasive methods in study II.

The AKI definition in study III differs from many recent studies, and it must be noted when results are interpreted. Study III included almost 200 patients, a reasonable amount. Nevertheless, an even larger number of patients would have been required to reach sufficient statistical power in many subgroup analyses. The low number of end points limited conducting a more comprehensive multivariable regression analysis. Despite a long study time of ten years, only 21 RRT patients were included, and we were unable to provide evidence from RRT and its association to AKI or mortality. The selection of patients to receive RRT was biased, and the decision to initiate RRT was made on an individual basis rather than by a structured algorithm. This had an effect on the outcome. Many patients succumbed who were withheld from receiving RRT. It is obvious that many of them would have likely succumbed despite RRT, but the decision to withhold RRT has potentially accelerated the poor outcome in some individuals.

We managed to gather only 32 individuals in study IV to perform a follow-up analysis, despite the long study period (over 27 years). Although average follow-up time was 7.4-9.3 years, it remained shortest (a little over a year) in those who were alive at the end of follow-up. As seen in study IV, the chronic impairment of kidney function may take many years or even decades to evolve, and because of this aspect, more impairments may have occurred, although full recovery of kidney function was noticed.

8. CONCLUSIONS

The following conclusions can be made based on studies I-IV

1. Plasma NGAL rises over time in nearly all burn patients. It showed a poor sensitivity and specificity to AKI and a lower diagnostic value than SCr or CysC. NGAL also reacted more slowly to deteriorating kidney function than SCr or CysC (I).

2. Plasma NT-proBNP correlated on cumulative infusions, older age and lower BMI during the first week after severe burn injury. A great variation in individual level was observed, with an even greater variation in patients with AKI. However, an association to AKI was not observed (II).

3. Increasing age, TBSA%, rhabdomyolysis and sepsis were risk factors for AKI. The probability of AKI increases along with increasing Baux score. The probability of death rises rapidly after Baux score 80; the increase is even greater in flame burns. The prognosis in major burns is relatively good without AKI, but AKI increases the likelihood of death during a hospital stay even in minor burns (III).

4. AKI is common in severe burns and is a considerable risk factor for mortality. In addition to AKI, increasing age and TBSA% are both major risk factors for death. A difference in in-hospital mortality was not seen between patients receiving RRT compared to the rest of the AKI patients. No significant difference was noticed in mortality between early and late AKI patients (III).

5. ABSI, Baux and modified Baux score are fair and equal predictors of mortality after severe burn injury. Their diminishing prediction power may be explained by improved burn care (III).

6. Risk for long-term impairment of kidney function is low for burn patients treated with RRT. Kidney function recovers in most patients before discharge from the burn unit. A minority of patients received RRT for a longer period of time, but the need for RRT subsided.

7. Severe AKI may accelerate underlying weakened kidney function to develop into CKD, but could not have been confirmed due to a small number of events and confounding factors during follow-up this (IV).

9. FUTURE ASPECTS

Plasma NGAL failed to achieve sufficient diagnostic value in primary diagnostics compared to SCr or CysC in study I. NGAL rose constantly in nearly all patients whether or not they had AKI. This suggests that an extrarenal component exists. The nature of the biomarker can be assessed again when laboratory diagnostics are capable of distinguishing renal NGAL from blood. More accurate and rapid means to establish ongoing AKI are desired to start interventions to avoid the loss of kidney function. Hopefully, some means will be available in the future. Currently there are no curative means to prevent ongoing AKI, but many therapies are investigated at the moment.

NT-proBNP turned out to be a potential biomarker to evaluate fluid resuscitation. Study II, however, showed a great patient-to-patient variation and a difference in tolerance to increased blood volume. Further investigations are needed to eliminate possible confounding factors and establish whether or not NT-proBNP could be utilized to tailor individual fluid resuscitation after severe burn injury. The amount of infused fluids is based on objective measurements rather than on a clinical estimate in an ideal situation.

Study III demonstrated AKI as a notable individual risk factor for death during a hospital stay after a severe burn injury. These results demand new methods for a faster diagnosis of AKI to establish interventions that prevent AKI from progressing and to improve the prognosis of burn victims through these means.

The number of patients staying dependent on RRT after severe burn injury was small in study IV. However, patients who are at an increased risk to develop CKD need to be recognized, and this risk needs to be mitigated by evidence-based interventions to avoid the permanent later loss of kidney function with its adverse outcomes.

Organizing a multiburn center study would increase the number of subjects included and therefore make it possible to reach sufficient statistical power. Investigating causality between interventions and AKI would require randomized trials and a large number of patients.

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